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(54) Title: COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF COLON CANCER AND METHODS FOR THEIR USE

### (57) Abstract

Compositions and methods for the therapy and diagnosis of cancer, such as colon cancer, are disclosed. Compositions may comprise one or more colon tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a colon tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as colon cancer. Diagnostic methods based on detecting a colon tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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# COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF COLON CANCER AND METHODS FOR THEIR USE

#### TECHNICAL FIELD

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The present invention relates generally to therapy and diagnosis of cancer, such as colon cancer. The invention is more specifically related to polypeptides comprising at least a portion of a colon tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of colon cancer, and for the diagnosis and monitoring of such cancers.

#### BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Colon cancer is the second most frequently diagnosed malignancy in the United States as well as the second most common cause of cancer death. An estimated 95,600 new cases of colon cancer will be diagnosed in 1998, with an estimated 47,700 deaths. The five-year survival rate for patients with colorectal cancer detected in an early localized stage is 92%; unfortunately, only 37% of colorectal cancer is diagnosed at this stage. The survival rate drops to 64% if the cancer is allowed to spread to adjacent organs or lymph nodes, and to 7% in patients with distant metastases.

The prognosis of colon cancer is directly related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement, consequently, early detection and treatment are especially important. Currently, diagnosis is aided by the use of screening assays for fecal occult blood, sigmoidoscopy, colonoscopy and double contrast barium enemas. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. Recurrence following surgery (the most common form of therapy) is a major problem and is often the

ultimate cause of death. In spite of considerable research into therapies for the disease, colon cancer remains difficult to diagnose and treat. In spite of considerable research into therapies for these and other cancers, colon cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

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Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as colon cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a colon tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-121, 123-197 and 205-486; (b) variants of a sequence recited in SEQ ID NO: 1-121, 123-197 and 205-486; and (c) complements of a sequence of (a) or (b).

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a colon tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a colon tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

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The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a colon tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a colon tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under

conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

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The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a colon tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expresses such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be colon cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a)

contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached figures. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### **SEQUENCE IDENTIFIERS**

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SEQ ID NO: 1 is a first determined cDNA sequence for Contig 1, showing homology to Neutrophil Gelatinase Associated Lipocalin.

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SEQ ID NO: 2 is the determined cDNA sequence for Contig 2, showing no significant homology to any known genes.

SEQ ID NO: 3 is the determined cDNA sequence for Contig 4, showing homology to Carcinoembryonic antigen.

SEQ ID NO: 4 is the determined cDNA sequence for Contig 5, showing homology to Carcinoembryonic antigen.

SEO ID NO: 5 is the determined cDNA sequence for Contig 9, showing homology to Carcinoembryonic antigen.

SEQ ID NO: 6 is the determined cDNA sequence for Contig 52, showing homology to Carcinoembryonic antigen.

SEQ ID NO: 7 is the determined cDNA sequence for Contig 6, showing homology toVillin.

SEQ ID NO: 8 is the determined cDNA sequence for Contig 8, showing no significant homology to any known genes.

SEQ ID NO: 9 is the determined cDNA sequence for Contig 10, showing homology to Transforming Growth Factor (BIGH3).

SEQ ID NO: 10 is the determined cDNA sequence for Contig 19, showing homology to Transforming Growth Factor (BIGH3).

SEQ ID NO: 11 is the determined cDNA sequence for Contig 21, showing homology to Transforming Growth Factor (BIGH3).

SEQ ID NO: 12 is the determined cDNA sequence for Contig 11, showing homology to CO-029.

SEQ ID NO: 13 is the determined cDNA sequence for Contig 55, showing homology to CO-029.

SEQ ID NO: 14 is the determined cDNA sequence for Contig 12, showing homology to Chromosome 17, clone hRPC.1171\_I\_10, also referred to as C798P.

SEQ ID NO: 15 is the determined cDNA sequence for Contig 13, showing no significant homology to any known gene.

SEQ ID NO: 16 is the determined cDNA sequence for Contig 14, also referred to as 14261, showing no significant homology to any known gene. 30

SEQ ID NO: 17 is the determined cDNA sequence for Contig 15, showing homology to Ets-Related Transcription Factor (ERT).

SEQ ID NO: 18 is the determined cDNA sequence for Contig 16, showing homology to Chromosome 5, PAC clone 228g9 (LBNL H142).

SEQ ID NO: 19 is the determined cDNA sequence for Contig 24, showing homology to Chromosome 5, PAC clone 228g9 (LBNL H142).

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SEQ ID NO: 20 is the determined cDNA sequence for Contig 17, showing homology to Cytokeratin.

SEQ ID NO: 21 is the determined cDNA sequence for Contig 18, showing homology to L1-Cadherin.

SEQ ID NO: 22 is the determined cDNA sequence for Contig 20, showing no significant homology to any known gene.

SEQ ID NO: 23 is the determined cDNA sequence for Contig 22, showing homology to Burnetanide-sensitive Na-K-Cl cotransporter (NKCCl).

SEQ ID NO: 24 is the determined cDNA sequence for Contig 23, showing no significant homology to any known gene.

SEQ ID NO: 25 is the determined cDNA sequence for Contig 25, showing homology to Macrophage Inflammatory Protein 3 alpha.

SEQ ID NO: 26 is the determined cDNA sequence for Contig 26, showing homology to Laminin.

SEQ ID NO: 27 is the determined cDNA sequence for Contig 48, showing homology to Laminin.

SEQ ID NO: 28 is the determined cDNA sequence for Contig 27, showing homology to Mytobularin (MTM1).

SEQ ID NO: 29 is the determined cDNA sequence for Contig 28, showing homology to Chromosome 16 BAC clone CIT987SK-A-363E6.

SEQ ID NO: 30 is the determined cDNA sequence for Contig 29, also referred to as C751P and 14247, showing no significant homology to any known gene, but partial homology to Rat GSK-3β-interacting protein Axil homolog.

SEQ ID NO: 31 is the determined cDNA sequence for Contig 30, showing homology to Zinc Finger Transcription Factor (ZNF207).

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SEQ ID NO: 32 is the determined cDNA sequence for Contig 31, showing no significant homology to any known gene, but partial homology to Mus musculus GOB-4 homolog.

SEQ ID NO: 33 is the determined cDNA sequence for Contig 35, showing no significant homology to any known gene, but partial homology to Mus musculus GOB-4 homolog.

SEQ ID NO: 34 is the determined cDNA sequence for Contig 32, showing no significant homology to any known gene.

SEQ ID NO: 35 is the determined cDNA sequence for Contig 34, showing homology to Desmoglein 2.

SEQ ID NO: 36 is the determined cDNA sequence for Contig 36, showing no significant homology to any known gene.

SEQ ID NO: 37 is the determined cDNA sequence for Contig 37, showing homology to Putative Transmembrane Protein.

SEQ ID NO: 38 is the determined cDNA sequence for Contig 38, also referred to as C796P and 14219, showing no significant homology to any known gene.

SEQ ID NO: 39 is the determined cDNA sequence for Contig 40, showing homology to Nonspecific Cross-reacting Antigen.

SEQ ID NO: 40 is the determined cDNA sequence for Contig 41, also referred to as C799P and 14308, showing no significant homology to any known gene.

SEQ ID NO: 41 is the determined cDNA sequence for Contig 42, also referred to as C794P and 14309, showing no significant homology to any known gene.

SEQ ID NO: 42 is the determined cDNA sequence for Contig 43, showing homology to Chromosome 1 specific transcript KIAA0487.

SEQ ID NO: 43 is the determined cDNA sequence for Contig 45, showing homology to hMCM2.

SEQ ID NO: 44 is the determined cDNA sequence for Contig 46, showing homology to ETS2.

SEQ ID NO: 45 is the determined cDNA sequence for Contig 49, showing homology to Pump-1.

SEQ ID NO: 46 is the determined cDNA sequence for Contig 50, also referred to as C792P and 18323, showing no significant homology to any known gene.

SEQ ID NO: 47 is the determined cDNA sequence for Contig 51, also referred to as C795P and 14317, showing no significant homology to any known gene.

SEQ ID NO: 48 is the determined cDNA sequence for 11092, showing no significant homology to any known gene.

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SEQ ID NO: 49 is the determined cDNA sequence for 11093, showing no significant homology to any known gene.

SEQ ID NO: 50 is the determined cDNA sequence for 11094, showing homology Human Putative Enterocyte Differentiation Protein.

SEQ ID NO: 51 is the determined cDNA sequence for 11095, showing homology to Human Transcriptional Corepressor hKAP1/TIF1B mRNA.

SEQ ID NO: 52 is the determined cDNA sequence for 11096, showing no significant homology to any known gene.

SEQ ID NO: 53 is the determined cDNA sequence for 11097, showing homology to Human Nonspecific Antigen.

SEQ ID NO: 54 is the determined cDNA sequence for 11098, showing no significant homology to any known gene.

SEQ ID NO: 55 is the determined cDNA sequence for 11099, showing homology to Human Pancreatic Secretory Inhibitor (PST) mRNA.

SEQ ID NO: 56 is the determined cDNA sequence for 11186, showing homology to Human Pancreatic Secretory Inhibitor (PST) mRNA.

SEQ ID NO: 57 is the determined cDNA sequence for 11101, showing homology to Human Chromosome X.

SEQ ID NO: 58 is the determined cDNA sequence for 11102, showing homology to Human Chromosome X.

SEQ ID NO: 59 is the determined cDNA sequence for 11103, showing no significant homology to any known gene.

SEQ ID NO: 60 is the determined cDNA sequence for 11174, showing no significant homology to any known gene.

SEQ ID NO: 61 is the determined cDNA sequence for 11104, showing homology to Human mRNA for KIAA0154.

- SEQ ID NO: 62 is the determined cDNA sequence for 11105, showing homology toHuman Apurinic/Apyrimidinic Endonuclease (hap1)mRNA.
- SEQ ID NO: 63 is the determined cDNA sequence for 11106, showing homology toHuman Chromosome 12p13.

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- SEQ ID NO: 64 is the determined cDNA sequence for 11107, showing homology to Human 90 kDa Heat Shock Protein.
- SEQ ID NO: 65 is the determined cDNA sequence for 11108, showing no significant homology to any known gene.
  - SEQ ID NO: 66 is the determined cDNA sequence for 11112, showing no significant homology to any known gene.
  - SEQ ID NO: 67 is the determined cDNA sequence for 11115, showing no significant homology to any known gene.
- SEQ ID NO: 68 is the determined cDNA sequence for 11117, showing no significant homology to any known gene.
  - SEQ ID NO: 69 is the determined cDNA sequence for 11118, showing no significant homology to any known gene.
- SEQ ID NO: 70 is the determined cDNA sequence for 11119, showing homology to Human Elongation Factor 1-alpha.
  - SEQ ID NO: 71 is the determined cDNA sequence for 11121, showing homology to Human Lamin B Receptor (LBR) mRNA.
  - SEQ ID NO: 72 is the determined cDNA sequence for 11122, showing homology to H. sapiens mRNA for Novel Glucocorticoid.
  - SEQ ID NO: 73 is the determined cDNA sequence for 11123, showing homology to H. sapiens mRNA for snRNP protein B.
    - SEQ ID NO: 74 is the determined cDNA sequence for 11124, showing homology to Human Cisplatin Resistance Associated Beta-protein.
- SEQ ID NO: 75 is the determined cDNA sequence for 11127, showing homology to M. musculus Calumenin mRNA.

SEQ ID NO: 76 is the determined cDNA sequence for 11128, showing homology to Human ras-related small GTP binding protein.

SEQ ID NO: 77 is the determined cDNA sequence for 11130, showing homology to Human Cosmid U169d2.

SEQ ID NO: 78 is the determined cDNA sequence for 11131, showing homology to H. sapiens mRNA for protein homologous to Elongation 1-g.

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SEQ ID NO: 79 is the determined cDNA sequence for 11134, showing no significant homology to any known gene.

SEQ ID NO: 80 is the determined cDNA sequence for 11135, showing homology to H. sapiens Nieman-Pick (NPC1) mRNA.

SEQ ID NO: 81 is the determined cDNA sequence for 11137, showing homology to H. sapiens mRNA for Niecin b-chain.

SEQ ID NO: 82 is the determined cDNA sequence for 11138, showing homology to Human Endogenous Retroviral Protease mRNA.

SEQ ID NO: 83 is the determined cDNA sequence for 11139, showing homology to H. sapiens mRNA for DMBT1 protein.

SEQ ID NO: 84 is the determined cDNA sequence for 11140, showing homology to H. sapiens ras GTPase activating-like protein.

SEQ ID NO: 85 is the determined cDNA sequence for 11143, showing homology to Human Acidic Ribosomal Phosphoprotein PO mRNA.

SEQ ID NO: 86 is the determined cDNA sequence for 11144, showing homology to H. sapiens U21 mRNA.

SEQ ID NO: 87 is the determined cDNA sequence for 11145, showing homology to Human GTP-binding protein.

SEQ ID NO: 88 is the determined cDNA sequence for 11148, showing homology to H. sapiens U21 mRNA.

SEQ ID NO: 89 is the determined cDNA sequence for 11151, showing no significant homology to any known gene.

SEQ ID NO: 90 is the determined cDNA sequence for 11154, showing no significant homology to any known gene.

- SEQ ID NO: 91 is the determined cDNA sequence for 11156, showing homology to H. sapiens Ribosomal Protein L27.
- SEQ ID NO: 92 is the determined cDNA sequence for 11157, showing homology to H. sapiens Ribosomal Protein L27.
- SEQ ID NO: 93 is the determined cDNA sequence for 11158, showing no significant homology to any known gene.
  - SEQ ID NO: 94 is the determined cDNA sequence for 11162, showing homology to Ag-X antigen.
- SEQ ID NO: 95 is the determined cDNA sequence for 11164, showing homology to H. sapiens mRNA for Signal Recognition Protein sub14.
  - SEQ ID NO: 96 is the determined cDNA sequence for 11165, showing homology to Human PAC 204e5/127h14.
  - SEQ ID NO: 97 is the determined cDNA sequence for 11166, showing homology to Human mRNA for KIAA0108.
- SEQ ID NO: 98 is the determined cDNA sequence for 11167, showing homology to H. sapiens mRNA for Neutrophil Gelatinase assct. Lipocalin.
  - SEQ ID NO: 99 is the determined cDNA sequence for 11168, showing no significant homology to any known gene.
- SEQ ID NO: 100 is the determined cDNA sequence for 11172, showing no significant homology to any known gene.
  - SEQ ID NO: 101 is the determined cDNA sequence for 11175, showing no significant homology to any known gene.
  - SEQ ID NO: 102 is the determined cDNA sequence for 11176, showing homology to Human maspin mRNA.
- SEQ ID NO: 103 is the determined cDNA sequence for 11177, showing homology to Human Carcinoembryonic Antigen.
  - SEQ ID NO: 104 is the determined cDNA sequence for 11178, showing homology to Human A-Tubulin mRNA.
- SEQ ID NO: 105 is the determined cDNA sequence for 11179, showing homology to
  Human mRNA for proton-ATPase-like protein.

- SEQ ID NO: 106 is the determined cDNA sequence for 11180, showing homology to Human HepG2 3' region cDNA clone hmd.
- SEQ ID NO: 107 is the determined cDNA sequence for 11182, showing homology to Human MHC homologous to Chicken B-Complex Protein.
- SEQ ID NO: 108 is the determined cDNA sequence for 11183, showing homology to Human High Mobility Group Box (SSRP1) mRNA.
  - SEQ ID NO: 109 is the determined cDNA sequence for 11184, showing no significant homology to any known gene.
  - SEQ ID NO: 110 is the determined cDNA sequence for 11185, showing no significant homology to any known gene.

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- SEQ ID NO: 111 is the determined cDNA sequence for 11187, showing no significant homology to any known gene.
- SEQ ID NO: 112 is the determined cDNA sequence for 11190, showing homology to Human Replication Protein A 70kDa.
- SEQ ID NO: 113 is the determined cDNA sequence for Contig 47, also referred to as C797P, showing homology to Human Chromosome X clone bWXD342.
  - SEQ ID NO: 114 is the determined cDNA sequence for Contig 7, showing homology to Equilibrative Nucleoside Transporter 2 (ent2).
  - SEQ ID NO: 115 is the determined cDNA sequence for 14235.1, also referred to as C791P, showing homology to H. sapiens chromosome 21 derived BAC containing ets-2 gene.
  - SEQ ID NO: 116 is the determined cDNA sequence for 14287.2, showing no significant homology to any known gene, but some degree of homology to Putative Transmembrane Protein.
- SEQ ID NO: 117 is the determined cDNA sequence for 14233.1, also referred to as Contig 48, showing no significant homology to any known gene.
  - SEQ ID NO: 118 is the determined cDNA sequence for 14298.2, also referred to as C793P, showing no significant homology to any known gene.
- SEQ ID NO: 119 is the determined cDNA sequence for 14372, also referred to as

  Contig 44, showing no significant homology to any known gene.

SEQ ID NO: 120 is the determined cDNA sequence for 14295, showing homology to secreted cement gland protein XAG-2 homolog.

SEQ ID NO: 121 is the determined full-length cDNA sequence for a clone showing homology to Beta IG-H3.

SEQ ID NO: 122 is the predicted amino acid sequence for the clone of SEQ ID NO: 121.

SEQ ID NO: 123 is a longer determined cDNA sequence for C751P.

SEQ ID NO: 124 is a longer determined cDNA sequence for C791P.

SEQ ID NO: 125 is a longer determined cDNA sequence for C792P.

SEQ ID NO: 126 is a longer determined cDNA sequence for C793P.

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SEQ ID NO: 127 is a longer determined cDNA sequence for C794P.

SEQ ID NO: 128 is a longer determined cDNA sequence for C795P.

SEQ ID NO: 129 is a longer determined cDNA sequence for C796P.

SEQ ID NO: 130 is a longer determined cDNA sequence for C797P.

SEQ ID NO: 131 is a longer determined cDNA sequence for C798P.

SEQ ID NO: 132 is a longer determined cDNA sequence for C799P.

SEQ ID NO: 133 is a first partial determined cDNA sequence for CoSub-3 (also known as 23569).

SEQ ID NO: 134 is a second partial determined cDNA sequence for CoSub-3 (also known as 23569).

SEQ ID NO: 135 is a first partial determined cDNA sequence for CoSub-13 (also known as 23579).

SEQ ID NO: 136 is a second partial determined cDNA sequence for CoSub-13 (also known as 23579).

SEQ ID NO: 137 is the determined cDNA sequence for CoSub-17 (also known as 23583).

SEQ ID NO: 138 is the determined cDNA sequence for CoSub-19 (also known as 23585).

SEQ ID NO: 139 is the determined cDNA sequence for CoSub-22 (also known as 23714).

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SEQ ID NO: 140 is the determined cDNA sequence for CoSub-23 (also known as 23715).

SEQ ID NO: 141 is the determined cDNA sequence for CoSub-26 (also known as 23717).

5 SEQ ID NO: 142 is the determined cDNA sequence for CoSub-33 (also known as 23724).

SEQ ID NO: 143 is the determined cDNA sequence for CoSub-34 (also known as 23725).

SEQ ID NO: 144 is the determined cDNA sequence for CoSub-35 (also known as 23726).

SEQ ID NO: 145 is the determined cDNA sequence for CoSub-37 (also known as 23728).

SEQ ID NO: 146 is the determined cDNA sequence for CoSub-39 (also known as 23730).

SEQ ID NO: 147 is the determined cDNA sequence for CoSub-42 (also known as 23766).

SEQ ID NO: 148 is the determined cDNA sequence for CoSub-44 (also known as 23768).

SEQ ID NO: 149 is the determined cDNA sequence for CoSub-47 (also known as 23771).

SEQ ID NO: 150 is the determined cDNA sequence for CoSub-54 (also known as 23778).

SEQ ID NO: 151 is the determined cDNA sequence for CoSub-55 (also known as 23779).

SEQ ID NO: 152 is the determined cDNA sequence for CT1 (also known as 24099).

SEQ ID NO: 153 is the determined cDNA sequence for CT2 (also known as 24100).

SEQ ID NO: 154 is the determined cDNA sequence for CT3 (also known as 24101).

SEQ ID NO: 155 is the determined cDNA sequence for CT6 (also known as 24104).

SEQ ID NO: 156 is the determined cDNA sequence for CT7 (also known as 24105).

SEQ ID NO: 157 is the determined cDNA sequence for CT12 (also known as 24110).

SEQ ID NO: 158 is the determined cDNA sequence for CT13 (also known as 24111).

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24805).

SEQ ID NO: 159 is the determined cDNA sequence for CT14 (also known as 24112). SEQ ID NO: 160 is the determined cDNA sequence for CT15 (also known as 24113). SEQ ID NO: 161 is the determined cDNA sequence for CT17 (also known as 24115). SEQ ID NO: 162 is the determined cDNA sequence for CT18 (also known as 24116). SEO ID NO: 163 is the determined cDNA sequence for CT22 (also known as 23848). SEQ ID NO: 164 is the determined cDNA sequence for CT24 (also known as 23849). SEQ ID NO: 165 is the determined cDNA sequence for CT31 (also known as 23854). SEQ ID NO: 166 is the determined cDNA sequence for CT34 (also known as 23856). SEQ ID NO: 167 is the determined cDNA sequence for CT37 (also known as 23859). SEQ ID NO: 168 is the determined cDNA sequence for CT39 (also known as 23860). SEQ ID NO: 169 is the determined cDNA sequence for CT40 (also known as 23861). SEQ ID NO: 170 is the determined cDNA sequence for CT51 (also known as 24130). SEQ ID NO: 171 is the determined cDNA sequence for CT53 (also known as 24132). SEQ ID NO: 172 is the determined cDNA sequence for CT63 (also known as 24595). SEQ ID NO: 173 is the determined cDNA sequence for CT88 (also known as 24608). SEQ ID NO: 174 is the determined cDNA sequence for CT92 (also known as 24800). SEQ ID NO: 175 is the determined cDNA sequence for CT94 (also known as 24802). SEQ ID NO: 176 is the determined cDNA sequence for CT102 (also known as

SEQ ID NO: 177 is the determined cDNA sequence for CT103 (also known as 24806).

SEQ ID NO: 178 is the determined cDNA sequence for CT111 (also known as 25520).

SEQ ID NO: 179 is the determined cDNA sequence for CT118 (also known as 25 25522).

SEQ ID NO: 180 is the determined cDNA sequence for CT121 (also known as 25523).

SEQ ID NO: 181 is the determined cDNA sequence for CT126 (also known as 25527).

SEQ ID NO: 182 is the determined cDNA sequence for CT135 (also known as 25534).

- SEQ ID NO: 183 is the determined cDNA sequence for CT140 (also known as 25537).
- SEQ ID NO: 184 is the determined cDNA sequence for CT145 (also known as 25542).
- SEQ ID NO: 185 is the determined cDNA sequence for CT147 (also known as 25543).
  - SEQ ID NO: 186 is the determined cDNA sequence for CT148 (also known as 25544).
- SEQ ID NO: 187 is the determined cDNA sequence for CT502 (also known as 10 26420).
  - SEQ ID NO: 188 is the determined cDNA sequence for CT507 (also known as 26425).
  - SEQ ID NO: 189 is the determined cDNA sequence for CT521 (also known as 27366).
- SEQ ID NO: 190 is the determined cDNA sequence for CT544 (also known as 27375).
  - SEQ ID NO: 191 is the determined cDNA sequence for CT577 (also known as 27385).
- SEQ ID NO: 192 is the determined cDNA sequence for CT580 (also known as 20 27387).
  - SEQ ID NO: 193 is the determined cDNA sequence for CT594 (also known as 27540).
  - SEQ ID NO: 194 is the determined cDNA sequence for CT606 (also known as 27547).
- SEQ ID NO: 195 is the determined cDNA sequence for CT607 (also known as 27548).
  - SEQ ID NO: 196 is the determined cDNA sequence for CT599 (also known as 27903).
- SEQ ID NO: 197 is the determined cDNA sequence for CT632 (also known as 27922).
  - SEQ ID NO: 198 is the predicted amino acid sequence for CT502 (SEQ ID NO: 187).

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SEQ ID NO: 199 is the predicted amino acid sequence for CT507 (SEQ ID NO: 188). SEQ ID NO: 200 is the predicted amino acid sequence for CT521 (SEQ ID NO: 189). SEQ ID NO: 201 is the predicted amino acid sequence for CT544 (SEQ ID NO: 190). SEQ ID NO: 202 is the predicted amino acid sequence for CT606 (SEQ ID NO: 194). SEQ ID NO: 203 is the predicted amino acid sequence for CT607 (SEQ ID NO: 195). 5 SEQ ID NO: 204 is the predicted amino acid sequence for CT632 (SEQ ID NO: 197). SEQ ID NO: 205 is the determined cDNA sequence for clone 25244. SEQ ID NO: 206 is the determined cDNA sequence for clone 25245. SEQ ID NO: 207 is the determined cDNA sequence for clone 25246. SEQ ID NO: 208 is the determined cDNA sequence for clone 25248. 10 SEQ ID NO: 209 is the determined cDNA sequence for clone 25249. SEQ ID NO: 210 is the determined cDNA sequence for clone 25250. SEQ ID NO: 211 is the determined cDNA sequence for clone 25251. SEQ ID NO: 212 is the determined cDNA sequence for clone 25252. SEQ ID NO: 213 is the determined cDNA sequence for clone 25253. 15 SEQ ID NO: 214 is the determined cDNA sequence for clone 25254. SEQ ID NO: 215 is the determined cDNA sequence for clone 25255. SEQ ID NO: 216 is the determined cDNA sequence for clone 25256. SEQ ID NO: 217 is the determined cDNA sequence for clone 25257. SEQ ID NO: 218 is the determined cDNA sequence for clone 25259. 20 SEQ ID NO: 219 is the determined cDNA sequence for clone 25260. SEQ ID NO: 220 is the determined cDNA sequence for clone 25261. SEQ ID NO: 221 is the determined cDNA sequence for clone 25262. SEQ ID NO: 222 is the determined cDNA sequence for clone 25263. SEQ ID NO: 223 is the determined cDNA sequence for clone 25264. 25 SEQ ID NO: 224 is the determined cDNA sequence for clone 25265. SEQ ID NO: 225 is the determined cDNA sequence for clone 25266. SEQ ID NO: 226 is the determined cDNA sequence for clone 25267. SEQ ID NO: 227 is the determined cDNA sequence for clone 25268. SEQ ID NO: 228 is the determined cDNA sequence for clone 25269. 30 SEQ ID NO: 229 is the determined cDNA sequence for clone 25271.

SEQ ID NO: 230 is the determined cDNA sequence for clone 25272. SEQ ID NO: 231 is the determined cDNA sequence for clone 25273. SEQ ID NO: 232 is the determined cDNA sequence for clone 25274. SEQ ID NO: 233 is the determined cDNA sequence for clone 25275. SEQ ID NO: 234 is the determined cDNA sequence for clone 25276. SEQ ID NO: 235 is the determined cDNA sequence for clone 25277. SEQ ID NO: 236 is the determined cDNA sequence for clone 25278. SEQ ID NO: 237 is the determined cDNA sequence for clone 25280. SEQ ID NO: 238 is the determined cDNA sequence for clone 25281. SEO ID NO: 239 is the determined cDNA sequence for clone 25282. SEQ ID NO: 240 is the determined cDNA sequence for clone 25283. SEQ ID NO: 241 is the determined cDNA sequence for clone 25284. SEQ ID NO: 242 is the determined cDNA sequence for clone 25285. SEQ ID NO: 243 is the determined cDNA sequence for clone 25286. SEQ ID NO: 244 is the determined cDNA sequence for clone 25287. SEQ ID NO: 245 is the determined cDNA sequence for clone 25288. SEQ ID NO: 246 is the determined cDNA sequence for clone 25289. SEO ID NO: 247 is the determined cDNA sequence for clone 25290. SEQ ID NO: 248 is the determined cDNA sequence for clone 25291. SEQ ID NO: 249 is the determined cDNA sequence for clone 25292. SEQ ID NO: 250 is the determined cDNA sequence for clone 25293. SEQ ID NO: 251 is the determined cDNA sequence for clone 25294. SEQ ID NO: 252 is the determined cDNA sequence for clone 25295. SEQ ID NO: 253 is the determined cDNA sequence for clone 25296. SEQ ID NO: 254 is the determined cDNA sequence for clone 25297. SEQ ID NO: 255 is the determined cDNA sequence for clone 25418. SEQ ID NO: 256 is the determined cDNA sequence for clone 25419. SEQ ID NO: 257 is the determined cDNA sequence for clone 25420. SEQ ID NO: 258 is the determined cDNA sequence for clone 25421. SEQ ID NO: 259 is the determined cDNA sequence for clone 25422. SEQ ID NO: 260 is the determined cDNA sequence for clone 25423.

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SEQ ID NO: 261 is the determined cDNA sequence for clone 25424. SEQ ID NO: 262 is the determined cDNA sequence for clone 25426. SEO ID NO: 263 is the determined cDNA sequence for clone 25427. SEQ ID NO: 264 is the determined cDNA sequence for clone 25428. SEQ ID NO: 265 is the determined cDNA sequence for clone 25429. SEQ ID NO: 266 is the determined cDNA sequence for clone 25430. SEQ ID NO: 267 is the determined cDNA sequence for clone 25431. SEQ ID NO: 268 is the determined cDNA sequence for clone 25432. SEQ ID NO: 269 is the determined cDNA sequence for clone 25433. SEQ ID NO: 270 is the determined cDNA sequence for clone 25434. SEQ ID NO: 271 is the determined cDNA sequence for clone 25435. SEQ ID NO: 272 is the determined cDNA sequence for clone 25436. SEQ ID NO: 273 is the determined cDNA sequence for clone 25437. SEQ ID NO: 274 is the determined cDNA sequence for clone 25438. SEQ ID NO: 275 is the determined cDNA sequence for clone 25439. SEQ ID NO: 276 is the determined cDNA sequence for clone 25440. SEQ ID NO: 277 is the determined cDNA sequence for clone 25441. SEQ ID NO: 278 is the determined cDNA sequence for clone 25442. SEQ ID NO: 279 is the determined cDNA sequence for clone 25443. SEQ ID NO: 280 is the determined cDNA sequence for clone 25444. SEQ ID NO: 281 is the determined cDNA sequence for clone 25445. SEQ ID NO: 282 is the determined cDNA sequence for clone 25446. SEQ ID NO: 283 is the determined cDNA sequence for clone 25447. SEQ ID NO: 284 is the determined cDNA sequence for clone 25448. SEQ ID NO: 285 is the determined cDNA sequence for clone 25844. 25 SEQ ID NO: 286 is the determined cDNA sequence for clone 25845. SEQ ID NO: 287 is the determined cDNA sequence for clone 25846. SEQ ID NO: 288 is the determined cDNA sequence for clone 25847. SEQ ID NO: 289 is the determined cDNA sequence for clone 25848. SEQ ID NO: 290 is the determined cDNA sequence for clone 25850. 30 SEQ ID NO: 291 is the determined cDNA sequence for clone 25851.

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SEQ ID NO: 292 is the determined cDNA sequence for clone 25852. SEQ ID NO: 293 is the determined cDNA sequence for clone 25853. SEO ID NO: 294 is the determined cDNA sequence for clone 25854. SEQ ID NO: 295 is the determined cDNA sequence for clone 25855. SEQ ID NO: 296 is the determined cDNA sequence for clone 25856. 5 SEQ ID NO: 297 is the determined cDNA sequence for clone 25857. SEO ID NO: 298 is the determined cDNA sequence for clone 25858. SEO ID NO: 299 is the determined cDNA sequence for clone 25859. SEQ ID NO: 300 is the determined cDNA sequence for clone 25860. SEQ ID NO: 301 is the determined cDNA sequence for clone 25861. 10 SEQ ID NO: 302 is the determined cDNA sequence for clone 25862. SEQ ID NO: 303 is the determined cDNA sequence for clone 25863. SEO ID NO: 304 is the determined cDNA sequence for clone 25864. SEO ID NO: 305 is the determined cDNA sequence for clone 25865. SEQ ID NO: 306 is the determined cDNA sequence for clone 25866. 15 -SEQ ID NO: 307 is the determined cDNA sequence for clone 25867. SEQ ID NO: 308 is the determined cDNA sequence for clone 25868. SEQ ID NO: 309 is the determined cDNA sequence for clone 25869. SEQ ID NO: 310 is the determined cDNA sequence for clone 25870. SEQ ID NO: 311 is the determined cDNA sequence for clone 25871. 20 SEO ID NO: 312 is the determined cDNA sequence for clone 25872. SEQ ID NO: 313 is the determined cDNA sequence for clone 25873. SEQ ID NO: 314 is the determined cDNA sequence for clone 25875. SEQ ID NO: 315 is the determined cDNA sequence for clone 25876. SEQ ID NO: 316 is the determined cDNA sequence for clone 25877. 25 SEQ ID NO: 317 is the determined cDNA sequence for clone 25878. SEQ ID NO: 318 is the determined cDNA sequence for clone 25879. SEQ ID NO: 319 is the determined cDNA sequence for clone 25880. SEQ ID NO: 320 is the determined cDNA sequence for clone 25881. SEQ ID NO: 321 is the determined cDNA sequence for clone 25882. 30 SEQ ID NO: 322 is the determined cDNA sequence for clone 25883.

SEO ID NO: 323 is the determined cDNA sequence for clone 25884. SEQ ID NO: 324 is the determined cDNA sequence for clone 25885. SEQ ID NO: 325 is the determined cDNA sequence for clone 25886. SEQ ID NO: 326 is the determined cDNA sequence for clone 25887. SEQ ID NO: 327 is the determined cDNA sequence for clone 25888. 5 SEQ ID NO: 328 is the determined cDNA sequence for clone 25889. SEQ ID NO: 329 is the determined cDNA sequence for clone 25890. SEO ID NO: 330 is the determined cDNA sequence for clone 25892. SEQ ID NO: 331 is the determined cDNA sequence for clone 25894. SEQ ID NO: 332 is the determined cDNA sequence for clone 25895. 10 SEO ID NO: 333 is the determined cDNA sequence for clone 25896. SEQ ID NO: 334 is the determined cDNA sequence for clone 25897. SEQ ID NO: 335 is the determined cDNA sequence for clone 25899. SEQ ID NO: 336 is the determined cDNA sequence for clone 25900. SEQ ID NO: 337 is the determined cDNA sequence for clone 25901. 15 SEQ ID NO: 338 is the determined cDNA sequence for clone 25902. SEQ ID NO: 339 is the determined cDNA sequence for clone 25903. SEQ ID NO: 340 is the determined cDNA sequence for clone 25904. SEQ ID NO: 341 is the determined cDNA sequence for clone 25906. SEQ ID NO: 342 is the determined cDNA sequence for clone 25907. 20 SEQ ID NO: 343 is the determined cDNA sequence for clone 25908. SEQ ID NO: 344 is the determined cDNA sequence for clone 25909. SEQ ID NO: 345 is the determined cDNA sequence for clone 25910. SEQ ID NO: 346 is the determined cDNA sequence for clone 25911. SEQ ID NO: 347 is the determined cDNA sequence for clone 25912. 25 SEQ ID NO: 348 is the determined cDNA sequence for clone 25913. SEQ ID NO: 349 is the determined cDNA sequence for clone 25914. SEQ ID NO: 350 is the determined cDNA sequence for clone 25915. SEQ ID NO: 351 is the determined cDNA sequence for clone 25916. SEQ ID NO: 352 is the determined cDNA sequence for clone 25917. 30 SEQ ID NO: 353 is the determined cDNA sequence for clone 25918.

SEQ ID NO: 354 is the determined cDNA sequence for clone 25919. SEQ ID NO: 355 is the determined cDNA sequence for clone 25920. SEQ ID NO: 356 is the determined cDNA sequence for clone 25921. SEQ ID NO: 357 is the determined cDNA sequence for clone 25922. SEQ ID NO: 358 is the determined cDNA sequence for clone 25924. SEQ ID NO: 359 is the determined cDNA sequence for clone 25925. SEQ ID NO: 360 is the determined cDNA sequence for clone 25926. SEQ ID NO: 361 is the determined cDNA sequence for clone 25927. SEQ ID NO: 362 is the determined cDNA sequence for clone 25928. SEQ ID NO: 363 is the determined cDNA sequence for clone 25929. SEQ ID NO: 364 is the determined cDNA sequence for clone 25930. SEQ ID NO: 365 is the determined cDNA sequence for clone 25931. SEQ ID NO: 366 is the determined cDNA sequence for clone 25932. SEQ ID NO: 367 is the determined cDNA sequence for clone 25933. SEQ ID NO: 368 is the determined cDNA sequence for clone 25934. SEQ ID NO: 369 is the determined cDNA sequence for clone 25935. SEQ ID NO: 370 is the determined cDNA sequence for clone 25936. SEQ ID NO: 371 is the determined cDNA sequence for clone 25939. SEQ ID NO: 372 is the determined cDNA sequence for clone 32016. SEQ ID NO: 373 is the determined cDNA sequence for clone 32021. SEQ ID NO: 374 is the determined cDNA sequence for clone 31993. SEQ ID NO: 375 is the determined cDNA sequence for clone 31997. SEQ ID NO: 376 is the determined cDNA sequence for clone 31942. SEQ ID NO: 377 is the determined cDNA sequence for clone 31937. SEQ ID NO: 378 is the determined cDNA sequence for clone 31952. SEQ ID NO: 379 is the determined cDNA sequence for clone 31992. SEQ ID NO: 380 is the determined cDNA sequence for clone 31961. SEQ ID NO: 381 is the determined cDNA sequence for clone 31964. SEQ ID NO: 382 is the determined cDNA sequence for clone 32005. SEQ ID NO: 383 is the determined cDNA sequence for clone 31980. SEQ ID NO: 384 is the determined cDNA sequence for clone 31940.

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SEQ ID NO: 385 is the determined cDNA sequence for clone 32004. SEQ ID NO: 386 is the determined cDNA sequence for clone 31956. SEQ ID NO: 387 is the determined cDNA sequence for clone 31934. SEQ ID NO: 388 is the determined cDNA sequence for clone 31998. SEQ ID NO: 389 is the determined cDNA sequence for clone 31973. SEQ ID NO: 390 is the determined cDNA sequence for clone 31976. SEQ ID NO: 391 is the determined cDNA sequence for clone 31988. SEQ ID NO: 392 is the determined cDNA sequence for clone 31948. SEQ ID NO: 393 is the determined cDNA sequence for clone 32013. SEQ ID NO: 394 is the determined cDNA sequence for clone 31986. SEQ ID NO: 395 is the determined cDNA sequence for clone 31954. SEQ ID NO: 396 is the determined cDNA sequence for clone 31987. SEQ ID NO: 397 is the determined cDNA sequence for clone 32029. SEQ ID NO: 398 is the determined cDNA sequence for clone 32028. SEQ ID NO: 399 is the determined cDNA sequence for clone 32012. SEQ ID NO: 400 is the determined cDNA sequence for clone 31959. SEQ ID NO: 401 is the determined cDNA sequence for clone 32027. SEQ ID NO: 402 is the determined cDNA sequence for clone 31957. SEQ ID NO: 403 is the determined cDNA sequence for clone 31950. SEO ID NO: 404 is the determined cDNA sequence for clone 32011. SEQ ID NO: 405 is the determined cDNA sequence for clone 32022. SEQ ID NO: 406 is the determined cDNA sequence for clone 32014. SEQ ID NO: 407 is the determined cDNA sequence for clone 31963. SEQ ID NO: 408 is the determined cDNA sequence for clone 31989. SEQ ID NO: 409 is the determined cDNA sequence for clone 32015. SEQ ID NO: 410 is the determined cDNA sequence for clone 32002. SEQ ID NO: 411 is the determined cDNA sequence for clone 31939. SEQ ID NO: 412 is the determined cDNA sequence for clone 32003. SEQ ID NO: 413 is the determined cDNA sequence for clone 31936. SEQ ID NO: 414 is the determined cDNA sequence for clone 32007. 30 SEQ ID NO: 415 is the determined cDNA sequence for clone 31965.

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SEQ ID NO: 416 is the determined cDNA sequence for clone 31935. SEQ ID NO: 417 is the determined cDNA sequence for clone 32008. SEQ ID NO: 418 is the determined cDNA sequence for clone 31966. SEQ ID NO: 419 is the determined cDNA sequence for clone 32020. SEQ ID NO: 420 is the determined cDNA sequence for clone 31971. SEQ ID NO: 421 is the determined cDNA sequence for clone 31977. SEQ ID NO: 422 is the determined cDNA sequence for clone 31985. SEQ ID NO: 423 is the determined cDNA sequence for clone 32023. SEQ ID NO: 424 is the determined cDNA sequence for clone 31981. SEQ ID NO: 425 is the determined cDNA sequence for clone 32006. SEQ ID NO: 426 is the determined cDNA sequence for clone 31991. SEQ ID NO: 427 is the determined cDNA sequence for clone 31995. SEQ ID NO: 428 is the determined cDNA sequence for clone 32000. SEQ ID NO: 429 is the determined cDNA sequence for clone 31990. SEQ ID NO: 430 is the determined cDNA sequence for clone 31946. SEQ ID NO: 431 is the determined cDNA sequence for clone 31938. SEQ ID NO: 432 is the determined cDNA sequence for clone 31941. SEQ ID NO: 433 is the determined cDNA sequence for clone 31982. SEQ ID NO: 434 is the determined cDNA sequence for clone 31996. SEQ ID NO: 435 is the determined cDNA sequence for clone 32010. SEQ ID NO: 436 is the determined cDNA sequence for clone 31974. SEQ ID NO: 437 is the determined cDNA sequence for clone 31983. SEQ ID NO: 438 is the determined cDNA sequence for clone 31999. SEQ ID NO: 439 is the determined cDNA sequence for clone 31949. SEQ ID NO: 440 is the determined cDNA sequence for clone 31947. SEQ ID NO: 441 is the determined cDNA sequence for clone 31994. SEQ ID NO: 442 is the determined cDNA sequence for clone 31958. SEQ ID NO: 443 is the determined cDNA sequence for clone 31975. SEQ ID NO: 444 is the determined cDNA sequence for clone 31984. SEQ ID NO: 445 is the determined cDNA sequence for clone 32024. SEQ ID NO: 446 is the determined cDNA sequence for clone 31972.

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SEQ ID NO: 447 is the determined cDNA sequence for clone 31943. SEQ ID NO: 448 is the determined cDNA sequence for clone 32018. SEQ ID NO: 449 is the determined cDNA sequence for clone 32026. SEQ ID NO: 450 is the determined cDNA sequence for clone 32009. SEQ ID NO: 451 is the determined cDNA sequence for clone 32019. SEQ ID NO: 452 is the determined cDNA sequence for clone 32025. SEQ ID NO: 453 is the determined cDNA sequence for clone 31967. SEQ ID NO: 454 is the determined cDNA sequence for clone 31968. SEQ ID NO: 455 is the determined cDNA sequence for clone 31955. SEQ ID NO: 456 is the determined cDNA sequence for clone 31951. SEQ ID NO: 457 is the determined cDNA sequence for clone 31970. SEQ ID NO: 458 is the determined cDNA sequence for clone 31962. SEQ ID NO: 459 is the determined cDNA sequence for clone 32001. SEQ ID NO: 460 is the determined cDNA sequence for clone 31953. SEQ ID NO: 461 is the determined cDNA sequence for clone 31944. SEQ ID NO: 462 is the determined cDNA sequence for clone 31825. SEQ ID NO: 463 is the determined cDNA sequence for clone 31828. SEQ ID NO: 464 is the determined cDNA sequence for clone 31830. SEQ ID NO: 465 is the determined cDNA sequence for clone 31841. SEQ ID NO: 466 is the determined cDNA sequence for clone 31847. SEQ ID NO: 467 is the determined cDNA sequence for clone 31850. SEQ ID NO: 468 is the determined cDNA sequence for clone 31852. SEQ ID NO: 469 is the determined cDNA sequence for clone 31855. SEQ ID NO: 470 is the determined cDNA sequence for clone 31858. SEQ ID NO: 471 is the determined cDNA sequence for clone 31861. SEQ ID NO: 472 is the determined cDNA sequence for clone 31868. SEQ ID NO: 473 is the determined cDNA sequence for clone 31870. SEQ ID NO: 474 is the determined cDNA sequence for clone 31872. SEQ ID NO: 475 is the determined cDNA sequence for clone 31873. SEQ ID NO: 476 is the determined cDNA sequence for clone 31877. SEQ ID NO: 477 is the determined cDNA sequence for clone 31878.

SEQ ID NO: 478 is the determined cDNA sequence for clone 31885.

SEQ ID NO: 479 is the determined cDNA sequence for clone 31888.

SEQ ID NO: 480 is the determined cDNA sequence for clone 31890.

SEQ ID NO: 481 is the determined cDNA sequence for clone 31893.

SEQ ID NO: 482 is the determined cDNA sequence for clone 31898.

SEQ ID NO: 483 is the determined cDNA sequence for clone 31901.

SEQ ID NO: 484 is the determined cDNA sequence for clone 31909.

SEQ ID NO: 485 is the determined cDNA sequence for clone 31910.

SEQ ID NO: 486 is the determined cDNA sequence for clone 31914.

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## DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as colon cancer. The compositions described herein may include colon tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a colon tumor protein or a variant thereof. A "colon tumor protein" is a protein that is expressed in colon tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain colon tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with colon cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human colon tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NO: 1-121, 123-197 and 205-486.

# 5 COLON TUMOR PROTEIN POLYNUCLEOTIDES

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Any polynucleotide that encodes a colon tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a colon tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a colon tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a colon tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native colon tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and

compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

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Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of

hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native colon tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a colon tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as colon tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a colon tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide

probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

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For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by

amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

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In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of colon tumor proteins are provided in SEQ ID NO: 1-121, 123-197 and 205-486. These polynucleotides were isolated from colon tumor cDNA libraries using conventional and/or PCR-based subtraction techniques, as described below.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a colon tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting

antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a colon tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

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A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In

general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

## COLON TUMOR POLYPEPTIDES

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Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a colon tumor protein or a variant thereof, as described herein. As noted above, a "colon tumor protein" is a protein that is expressed by colon tumor cells. Proteins that are colon tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with colon cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or

heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a colon tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

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Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. immunogenic portion of a native colon tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native colon tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native colon tumor protein in one or more substitutions, deletions, additions and/or insertions, such

that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

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Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain non-conservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

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Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A

fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

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Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and

second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

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Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid

proteins containing the C-LYTA fragment at the amino terminus has been described (see Biotechnology 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

### **BINDING AGENTS**

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The present invention further provides agents, such as antibodies and antigenbinding fragments thereof, that specifically bind to a colon tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a colon tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a colon tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as colon cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a colon tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies

this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

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Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example,

from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

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Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid.

Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

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Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

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### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a colon tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the ISOLEX<sup>TM</sup> system, available from

Nexell Therapeutics Inc., Irvine, CA. Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a colon tumor polypeptide, polynucleotide encoding a colon tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a colon tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

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T cells are considered to be specific for a colon tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the T cell specificity may be evaluated using any of a variety of standard polypeptide. techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a colon tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a colon tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Colon tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a colon tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* 

or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a colon tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a colon tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a colon tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

### PHARMACEUTICAL COMPOSITIONS AND VACCINES

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Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the

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necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and

5,075,109.

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Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically biodegradable microspheres; polyphosphazenes; derivatized polysaccharides; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT) (see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably OS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the OS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

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The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical

compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

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Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency, and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see Zitvogel et al.*, *Nature Med. 4:*594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a colon tumor protein (or portion or other variant thereof) such that the colon tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the colon tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a nonconjugated immunological partner, separately or in the presence of the polypeptide.

### **CANCER THERAPY**

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as colon cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or

may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

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Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive

polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to nonvaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient,

but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a colon tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

### METHODS FOR DETECTING CANCER

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In general, a cancer may be detected in a patient based on the presence of one or more colon tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as colon cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a colon tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of

the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length colon tumor proteins and portions thereof to which the binding agent binds, as described above.

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The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

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In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with colon cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>™</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

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The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as colon cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered

positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

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In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of Concentration of second binding agent at the area of immobilized binding agent. immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use colon tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such colon tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a colon tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a colon tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with one or more representative polypeptides (e.g., 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of colon tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

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As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a colon tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a colon tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the colon tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a colon tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a colon tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will

hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-121, 123-197 and 205-486. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

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One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may

also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple colon tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

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### **DIAGNOSTIC KITS**

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a colon tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a colon tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a colon tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a colon tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

#### **EXAMPLES**

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### Example 1

# ISOLATION AND CHARACTERIZATION OF COLON TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION AND MICROARRAY ANALYSIS

A cDNA library was constructed in the PCR2.1 vector (Invitrogen, Carlsbad, CA) by subtracting a pool of three colon tumors with a pool of normal colon, spleen, brain, liver, kidney, lung, stomach and small intestine using PCR subtraction methodologies (Clontech, Palo Alto, CA). The subtraction was performed using a PCR-based protocol, which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs, and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not

hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are over-expressed in colon tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

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To characterize the complexity and redundancy of the subtracted library, 96 clones were randomly picked and 65 were sequenced, as previously described. These sequences were further characterized by comparison with the most recent Genbank database (April, 1998) to determine their degree of novelty. No significant homologies were found to 21 of these clones, hereinafter referred to as 11092, 11093, 11096, 11098, 11103, 11174, 11108, 11112, 11115, 11117, 11118, 11134, 11151, 11154, 11158, 11168, 11172, 11175, 11184, 11185 and 11187. The determined cDNA sequences for these clones are provided in SEQ ID NO: 48, 49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101 and 109-111, respectively.

Two-thousand clones from the above mentioned cDNA subtraction library were randomly picked and submitted to a round of PCR amplification. Briefly, 0.5 µl of glycerol stock solution was added to 99.5 µl of pcr MIX (80 µl H<sub>2</sub>0, 10 µl 10X PCR Buffer, 6 μl 25 mM MgCl<sub>2</sub>, 1 μl 10 mM dNTPs, 1 μl 100 mM M13 forward primer primer (CACGACGTTGTAAAACGACGG), 1 μl 100 mM M13 reverse (CACAGGAAACAGCTATGACC)), and 0.5 µl 5 u/ml Taq polymerase (primers provided by (Operon Technologies, Alameda, CA). The PCR amplification was run for thirty cycles under the following conditions: 95°C for 5 min., 92°C for 30 sec., 57°C for 40 sec., 75°C for 2 min. and 75°C for 5 minutes.

mRNA expression levels for representative clones were determined using microarray technology (Synteni, Palo Alto, CA) in colon tumor tissues (n=25), normal colon tissues (n=6), kidney, lung, liver, brain, heart, esophagus, small intestine, stomach, pancreas, adrenal gland, salivary gland, resting PBMC, activated PBMC, bone marrow, dendritic cells, spinal cord, blood vessels, skeletal muscle, skin, breast and fetal tissues. The number of tissue samples tested in each case was one (n=1), except where specifically noted above; additionally, all the above-mentioned tissues were derived from humans. The PCR

amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, and fluorescent-labeled cDNA probes were generated by reverse transcription according to the protocol provided by Synteni. The microarrays were probed with the labeled cDNA probes, the slides scanned, and fluorescence intensity was measured. This intensity correlates with the hybridization intensity.

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One hundred and forty nine clones showed two or more fold over-expression in the colon tumor probe group as compared to the normal tissue probe group. These cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A and/or Model 377 (Foster City, CA). These sequences were compared to known sequences in the most recent GenBank database. No significant homologies to human gene sequences were found in forty nine of these clones, represented by the following sixteen cDNA consensus sequences: SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46 and 47, hereinafter referred to as Contig 2, 8, 13, 14, 20, 23, 29, 31, 35, 32, 36, 38, 41, 42, 50 and 51, respectively). Contig 29 (SEQ ID NO: 30) was found to be a Rat GSK-3-β-interacting protein Axil homolog. Also, Contigs 31 and 35 (SEQ ID NO: 32 and 33, respectively) were found to be a Mus musculus GOB-4 homolog. The determined cDNA sequences of SEQ ID NO: 1, 3-7, 9-14, 17-21, 23, 25-29, 31, 35, 37, 39, 42-45, 50, 51, 53, 55-58, 61-64, 70-78, 80-88, 91, 92, 94-98, 102-108 and 112 were found to show some homology to previously identified genes sequences.

Microarray analysis demonstrated Contig 2 (SEQ ID NO: 2) showed over-expression in 34% of colon tumors tested, as well as increased expression in normal pancreatic tissue, with no over-expression in normal colon tissues. Upon further analysis, Contigs 2, 8 and 23 were found to share homology to the known gene GW112. Contigs 4, 5, 9 and 52 showed homology to carcinoembryonic antigen (SEQ ID NO: 3, 4, 5 and 6, respectively). A representative sampling of these fragments showed over-expression in 85% of colon tumors, with over-expression in normal bone marrow and 3/6 normal colon tissues. Contig 6 (SEQ ID NO: 7), showing homology to the known gene sequence for villin, and was over-expressed in about half of all colon tumors tested, with a limited degree of low level over-expression in normal colon. Contig 12 (SEQ ID NO: 14), showing homology to Chromosome 17, clone hRPC.1171\_I\_10, also referred to as C798P, was over-expressed in

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approximately 70% of colon tumors tested, with low over-expression in 1/6 normal colon samples. Contig 14, also referred to as 14261 (SEQ ID NO: 16), showing no significant homology to any known gene, showed over-expression in 44% of colon tumors tested, with low level expression in half of normal colon tissues, as well as small intestine and pancreatic tissue. Contig 18 (SEQ ID NO: 21), showing homology to the known gene for L1-cadherin, showed over-expression in approximately half of colon tumors and low level over-expression in 3/6 normal colon tissues tested. Contig 22 (SEQ ID NO: 23), showing homology to Bumetanide-sensitive Na-K-Cl cotransporter was over-expressed in 70% of colon tumors and no over-expression in all normal tissues tested. Contig 25 (SEQ ID NO: 25), showing homology to macrophage inflammatory protein-3a, was over-expressed in over 40% of colon tumors and in activated PBMC. Contigs 26 and 48 (SEQ ID NOS: 25 and 26), showing homology to the sequence for laminin, was over-expressed in 48% of colon tumors and with low over-expression in stomach tissue. Contig 28 (SEQ ID NO: 29), showing homology to the known gene sequence for Chromosome 16 BAC clone CIT987SK-A-363E6, was overexpressed in 33% of colon tumors tested with normal stomach and 2/6 normal colon tissues showing low level over-expression. Contigs 29, 31 and 35 (SEQ ID NOS: 30, 32 and 33, respetively), also referred to as C751P, an unknown sequence showing limited and partial homology to Rat GSK-3β-interacting protein Axil homolog.and Mus musculus GOB-4 homolog, was over-expressed in 74% of colon tumors and no over-expression in all normal tissues tested. Contig 34 (SEQ ID NO: 35), showing homology to the known sequence for desmoglein 2, was over-expressed in 56% of colon tumors and showed low level overexpression in 1/6 normal colon tissues. Contig 36 (SEQ ID NO: 36), an unknown sequence also referred to as C793P, showed over-expression in 30% of colon tumor tissues tested. Contig 37 and 14287.2 (SEQ ID NOS: 37 and 116), an unknown sequence, but with limited (89%) homology to the known sequence for putative transmembrane protein was overexpressed in 70% of colon tumors, as well as in normal lung tissue and 3/6 normal colon tissues tested. Contig 38, also referred to as C796P and 14219 (SEQ ID NO: 38), showing no significant homology to any known gene, was over-expressed in 38% in colon tumors and no elevated over-expression in any normal tissues. Contig 41 (SEQ ID NO: 40), also referred to as C799P and 14308, an unknown sequence showing no significant homology to any known gene, was over-expressed in 22% of colon tumors. Contig 42, (SEQ ID NO: 41), also

referred to as C794P and 14309, an unknown sequence with no significant homology to any known gene, was over-expressed in 63% of colon tumors tested, as well as in 3/6 normal colon tissues. Contig 43 (SEQ ID NO: 42), showing homology to the known sequence for Chromosome 1 specific transcript KIAA0487 was over-expressed in 85% of colon tumors tested and in normal lung and 4/6 normal colon tissues. Contig 49 (SEQ ID NO: 45), showing homology to the known sequence for pump-1, was over-expressed in 44% of colon tumors and no over-expression in all normal tissues tested. Contig 50 (SEQ ID NO: 46), also referred to as C792P and 18323, showing no significant homology to any known gene, was over-expressed in 33% of colon tumors with no detectable over-expression in any normal tissues tested. Contig 51 (SEQ ID NO: 47), also referred to as C795P and 14317 was over-expressed in 11% of colon tumors.

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Additional microarray analysis yielded seven clones showing two or more fold overexpression in the colon tumor probe group as compared to the normal tissue probe group. Three of these clones demonstrated particularly good colon tumor specificity, and are represented by SEQ ID NO: 115, 116 and 120. Specifically, SEQ ID NO: 115, referred to as C791P or 14235, which shows homology to the known gene sequence for H. sapiens chromosome 21 derived BAC containing ets-2 gene, was over-expressed in 89% of colon tumors tested and in 5/6 normal colon tissues, as well as over-expressed at low levels in normal lung and activated PBMC. Microarray analysis for SEQ ID NO: 116 is discussed above. SEQ ID NO: 120, referred to as 14295, showing homology to the known gene sequence for secreted cement gland protein XAG-2 homolog, was over-expressed in 70% of colon tumors and in 5/6 normal colon tissues, as well as low level over-expression in normal small intestine, stomach and lung. All clones showing over-expression in colon tumor were sequenced and these sequences compared to the most recent Genbank database (February 12, 1999). Of the seven clones, three contained sequences that did not share significant homology to any known gene sequences, represented by SEQ ID NO: 116, 117 and 119. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in colon. The determined cDNA sequences of the remaining clones (SEQ ID NO: 113-115 and 120) were found to show some homology to previously identified genes.

Further analysis identified a clone which was recovered several times by PCR subtraction and by expression screening using a mouse anti-scid antiserum. The determined

full length cDNA sequence for this clone is provided in SEQ ID NO: 121, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 122. This clone is homologous with the known gene Beta IG-H3, as disclosed in U.S. Patent No. 5,444,164. Microarray analysis demonstrated this clone to be over-expressed in 75 to 80% of colon tumors tested (n=27), with no over-expression in normal colon samples (n=6), but with some low level over-expression in other normal tissues tested.

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Further analysis of the PCR-subtraction library described above led to the isolation of longer cDNA sequences for the clones of SEQ ID NO: 30, 115, 46, 118, 41, 47, 38, 113, 14 and 40 (known as C751P, C791P, C792P, C793P, C794P, C795P, C796P, C797P, C798P and C799P, respectively). These determined cDNA sequences are provided in SEQ ID NO: 123-132, respectively.

above with minor Using PCR subtraction methodology described modifications, transcripts from a pool of three moderately differentiated colon adenocarcinoma samples were subtracted with a set of transcripts from normal brain, pancreas, bone marrow, liver, heart, lung, stomach and small intestine. Modifications of the above protocol were included at the cDNA digestion steps and in the tester to drive hybridization ratios. In a first subtraction, the restriction enzymes PvuII, DraI, MscI and StuI were used to digest cDNAs, and the tester to driver ratio was 1:40, as suggested by Clontech. In a second subtraction, Dral, MscI and StuI were used for cDNA digestion and a tester to driver ratio of 1:76 was used. Following the PCR amplification steps, the cDNAs were clones into pCR2.1 plasmid vector. The determined cDNA sequences of 167 isolated clones are provided in SEQ ID NO: 205-371. These sequences were compared to sequences in the public databases as described above. The sequences of SEQ ID NO: 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369 and 371 were found to show some homology to previously identified ESTs. The remaining sequences were found to show some homology to previously identified genes.

Using the PCR subtraction technology described above, a cDNA library from a pool of primary colon tumors was subtracted with a cDNA library prepared from normal tissues, including brain, bone marrow, kidney, heart, lung, liver, pancreas, small intestine,

stomach and trachea. The determined cDNA sequences for 90 clones isolated in this subtraction are provided in SEQ ID NO: 372-461. Comparison of these sequences with those in the public databases as described above, revealed no homologies to the sequences of SEQ ID NO: 426, 445 and 453. The sequences of SEQ ID NO: 372-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455 and 457-461 showed some homology to previously identified genes, while the sequences of SEQ ID NO: 379, 405, 407, 408, 418, 424, 430-432, 437, 442, 444, 452 and 456 showed some homology to previously isolated ESTs.

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### Example 2

## ISOLATION OF TUMOR POLYPEPTIDES USING SCID-PASSAGED TUMOR RNA

Human colon tumor antigens were obtained using SCID mouse passaged colon tumor RNA as follows. Human colon tumor was implanted in SCID mice and harvested, as described in Patent Application Serial No. 08/556,659 filed 11/13/95, U.S. Patent No. 5,986,170. First strand cDNA was synthesized from poly A+ RNA from three SCID mouse-passaged colon tumors using a Lambda ZAP Express cDNA synthesis kit (Stratagene). The reactions were pooled and digested with RNase A, T1 and H to cleave the RNA and then treated with NaOH to degrade the RNA. The resulting cDNA was annealed with biotinylated (Vector Labs, Inc., Burlingame, CA) cDNA from a normal resting PBMC plasmid library (constructed from Superscript plasmid System, Gibco BRL), and subtracted with streptavidin by phenol/chloroform extraction. Second strand cDNA was synthesized from the subtracted first strand cDNA and digested with S1 nuclease (Gibco BRL). The cDNA was blunted with Pfu polymerase and EcoRI adaptors (Stratagene) were ligated to the The cDNA was phosphorylated with T4 polynucleotide kinase, digested with ends. restriction endonuclease XhoI, and size selected with Sephacryl S-400 (Sigma). Fractions were pooled, ligated to Lambda ZAP Express arms (Stratagene) and packaged with Gigapack Random plaques were picked, phagemid was excised, Gold III extract (Stratagene). transformed into XLOLR cells (Stratagene) and resulting plasmid DNA (Qiagen Inc., Valencia, CA) was sequenced as described above. The determined cDNA sequences for 17

clones isolated as described above are provided in SEQ ID NO: 133-151, wherein 133 and 134 represent partial sequences of a clone referred to as CoSub-3 and SEQ ID NO: 135 and 136 represent partial sequences of a clone referred to as CoSub-13. These sequences were compared with those in the public databases as described above. The sequences of SEQ ID NO: 139 and 149 showed no significant homologies to any previously identified sequences. The sequences of SEQ ID NO: 138, 140, 141, 142, 143, 148 and 149 showed some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 133-137, 144-147, 150 and 151 showed some homology to previously isolated gene sequences.

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### Example 3

## USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING COLON TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding colon tumor antigens by screening of colon tumor cDNA libraries with mouse anti-tumor sera.

A cDNA expression library was prepared from SCID mouse-passaged human colon tumor poly A+ RNA using a Stratagene (La Jolla, CA) Lambda ZAP Express kit, following the manufacturer's instructions. Sera was obtained from the colon tumor-bearing SCID mouse. This serum was injected into normal mice to produce anti-colon tumor serum. Approximately 600,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), positive plaques were identified. Phage was purified and phagemid excised for several clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 46 of the isolated clones are provided in SEQ ID NO: 152-197. The predicted amino acid sequences for the cDNA sequences of SEQ ID NO: 187, 188, 189, 190, 194, 195 and 197 are provided in SEQ ID NO: 198-204, respectively. The determined cDNA sequences were compared with those in the public database as described above. The sequences of SEQ ID NO: 156, 168, 184, 189, 192 and 196 showed some homology to previously isolated ESTs. The sequences of SEQ ID NO: 152-

155, 157-167, 169-182, 183, 185-188, 190, 194, 195 and 197 showed some homology to previously identified genes.

### Example 4

## ISOLATION AND CHARACTERIZATION OF COLON TUMOR POLYPEPTIDES BY CONVENTIONAL SUBTRACTION

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Two cDNA libraries were constructed and used to create a subtracted cDNA library as follows.

Using the GibcoBRL Superscript Plasmid System with minor modifications, two cDNA libraries were created. The first library, referred to as CTCL, was prepared from a pool of mRNA samples from three colon adenocarcinoma tissue samples. Two of the samples were described as Duke's stage C and one as Duke's stage B. All three samples were grade III in histological status. A second library (referred to as DriverLibpcDNA3.1+) was prepared from a pool of normal tissues, namely liver, pancreas, skin, bone marrow, resting PBMC, stomach and brain. Both libraries were prepared using the manufacturer's instructions with the following modifications: an EcoRI-NotI 5' cDNA adapter was used instead of the provided reagent; the vector pCDNA3.1(+) (Invitrogen) was substituted for the pSPORT vector; and the ligated DNA molecules were transformed into ElectroMaxDH10B electrocompetent cells. Clones from the libraries were analyzed by restriction digest and sequencing to determine average insert size, quality of the library and complexity of the library. DNA was prepared from each library and digested.

The driver DNA was biotinylated and hybridized with the colon library tester DNA at a ratio of 10:1. After two rounds of hybridizations, streptavidin incubations and extractions, the remaining colon cDNAs were size-selected by column chromatography and cloned into the pCMV-Script vector from Stratagene. Clones from this subtracted library (referred to as CTCL-S1) were characterized as described above for the unsubtracted libraries.

The determined cDNA sequences for 18 clones isolated from the CTCL-S1 library are provided in SEQ ID NO: 462-479. Comparison of these sequences with those in the public databases, as described above, revealed no significant homologies to the sequences

of SEQ ID NO: 476, 477 and 479. The remaining sequences showed some homology to previously identified genes.

In further studies, a cDNA library was prepared from a pool of mRNA from three metastatic colon adenocarcinomas derived from liver tissue samples. All samples were described as Duke's stage D. Conventional subtraction was performed as described above, using the DriverLibpcDNA3.1+ library described above as the driver. The resulting subtracted library (referred to as CMCL-S1) was characterized by isolating a set of clones for restriction analysis and sequencing.

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The determined cDNA sequences for 7 clones isolated from the CMCL-S1 library are provided in SEQ ID NO: 480-486. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequence of SEQ ID NO: 483. The sequences of SEQ ID NO: 480-482 and 484-486 were found to show some homology to previously identified genes.

## Example 5 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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## **CLAIMS**

- 1. An isolated polypeptide comprising at least an immunogenic portion of a colon tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
  - (a) sequences recited in SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483;
  - (b) sequences that hybridize to a sequence of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 under moderately stringent conditions; and
  - (c) a complement of a sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168,

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- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 122 and 198-204.
- An isolated polynucleotide encoding at least 15 amino acid residues of 4. 10 a colon tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 15 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 20 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 or a complement of any of the foregoing sequences.
- 5. An isolated polynucleotide encoding a colon tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303,

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- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483.
- 7. An isolated polynucleotide comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 under moderately stringent conditions.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
  - 9. An expression vector comprising a polynucleotide according to any one of claims claim 4-8.
- 30 10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a colon tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 or a complement of any of the foregoing polynucleotide sequences.

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- 12. A fusion protein comprising at least one polypeptide according to claim 1.
  - 13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
  - 14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.
  - 16. An isolated polynucleotide encoding a fusion protein according to claim 12.
- 17. A pharmaceutical composition comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

- (a) a polypeptide according to claim 1;
- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;

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- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.
- 18. A vaccine comprising an immunostimulant and at least one component selected from the group consisting of:
  - (a) a polypeptide according to claim 1;
  - (b) a polynucleotide according to claim 4;
  - (c) an antibody according to claim 11;
  - (d) a fusion protein according to claim 12; and
  - (e) a polynucleotide according to claim 16.
- 19. A vaccine according to claim 18, wherein the immunostimulant is an adjuvant.
  - 20. A vaccine according to any claim 18, wherein the immunostimulant induces a predominantly Type I response.
  - 21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.
  - 22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 20.
  - 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with an immunostimulant.
  - 26. A vaccine according to claim 25, wherein the immunostimulant is an adjuvant.
- 10 27. A vaccine according to claim 25, wherein the immunostimulant induces a predominantly Type I response.
  - 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.

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- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide encoded by a polynucleotide recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486, and thereby inhibiting the development of a cancer in the patient.
- 30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.
- 31. A method according to any one of claims 21, 22 and 29, wherein the cancer is colon cancer.
  - 32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
    - (i) polynucleotides recited in any one of SEQ ID NO: 1-121, 123-

197 and 205-486; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

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- 33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.
- 34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
  - 35. A method for stimulating and/or expanding T cells specific for a colon tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
    - (i) a polypeptide according to claim 1;
    - (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NO: 1-121, 123-197 and 205-486;
    - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and
    - (iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii), under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.
- 36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.
  - 37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.

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38. A method for inhibiting the development of a cancer in a patient,

comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with at least one component selected from the group consisting of:

- (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NO: 1-121, 123-197 and 205-486;
- (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or

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such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 39. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
  - (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
    - (i) a polypeptide according to claim 1;
    - (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NO: 1-121, 123-197 and 205-486;
    - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and
    - (iii) an antigen-presenting cell that expresses a polypeptide of (i) or

25 (ii);

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such that T cells proliferate;

- (b) cloning at least one proliferated cell to provide cloned T cells; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
  - 40. A method for determining the presence or absence of a cancer in a

patient, comprising the steps of:

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- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient:
  - 41. A method according to claim 40, wherein the binding agent is an antibody.
  - 42. A method according to claim 43, wherein the antibody is a monoclonal antibody.
    - 43. A method according to claim 40, wherein the cancer is colon cancer.
  - 44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
  - (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486 or a complement of any of the foregoing polynucleotides;
  - (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
  - (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

- 45. A method according to claim 44, wherein the binding agent is an antibody.
  - 46. A method according to claim 45, wherein the antibody is a monoclonal antibody.
  - 47. A method according to claim 44, wherein the cancer is a colon cancer.

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- 48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
  - (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
  - 50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
    - 51. A method for monitoring the progression of a cancer in a patient,

comprising the steps of:

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(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-121, 123-197 and 205-486 or a complement of any of the foregoing polynucleotides;

- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
  - (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
  - 53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

54. A diagnostic kit, comprising:

- (a) one or more antibodies according to claim 11; and
- (b) a detection reagent comprising a reporter group.
- 25 55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.
  - 56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
    - 57. A kit according to claim 54, wherein the reporter group is selected

from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

- 58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a colon tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483 or a complement of any of the foregoing polynucleotides.
  - 59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479 and 483.

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- 60. A diagnostic kit, comprising:
- (a) an oligonucleotide according to claim 59; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

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## SEQUENCE LISTING

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cageteatea gteaggaete geetgeecae catatggtaa gesgraggge atttgageag	360
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caaaagcaca gaagcacatc acatacacca gcaaggtttc caactactgc actgattaac
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tagatactet caatagettt tetatagete gteetagaaa aaaaaattaa atttteattt
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tggacaatga gagaaaagaa aaagcaggtg cctcatcnnc agatccttnt ggtatttatn
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tgccangtnc nanntaatnc atanaaag
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<211> 408

<212> DNA

## <213> Homo sapien

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agaataaccc tgatctttac ttaaaggagt tgctaaatct	tgctgaaaac aataaaggga 240
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gatactcaac tcaaatattt tgaaaaacag tttgaactgt	cagaacaaac aaaattacca 360
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cagagcactc cctaatttat gtgctatata aatatgtcag	
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ccagtgggct gatgctggga cccttaggat ggggctccca	5
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caagttgttt ggacagaaag gctacagagt gtggtcctgg	
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ctacatcctc actgactttc gcttggaata cgtgttggga aaattgaggt qcttcattca
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gagcagccac ctacttcaaa cccagcaccc gcagattgtg caggctgcgt cttcaqcacc
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agcacttgaa actgactctt cccctccacc atatagtagt attactggtg gaagtaccta
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caacttcaga tacagaagtt tacggtgagt tttatcccgt gccacctccc tatagcgttg
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gaagtttggc tggatcaagg gtgtattagt acgttgtatg ttaaacattt ggggtgtgat
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gcttttcatt agattgtcat ggattgtggg tcaagctgga ataggtctat cagtccttgt
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                                                                       251
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С
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 ttaaaaaata gcttgttgct tgcaanaaag tccatataat cttattcccc cccaaatata
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 attttatact ttgcactaaa ccaaaatagc ttatggaaaa ttagtattaa atagctaaac
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                                                                        401
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     <213> Homo sapien
     <400> 34
aacaatggct atgaaggcat tgtcgttgca atcgacccca atgtgccaga agatgaaaca
                                                                        60
ctcattcaac aaataaagga catggtgacc caggcatctc tgtatctgtt tgaagctaca
                                                                       120
qqaaaqcqat tttatttcaa aaatgttgcc attttgattc ctgaaacatg gaagacaaag
                                                                       180
                                                                       240
qctqactatg tgagaccaaa acttgagacc tacaaaaatg ctgatgttct ggttgcttga
gtctactcct ccaggtaatg atgaacccta cactgagcag atggggcaac tgtggagaga
                                                                       300
aggggtgaaa ggatcccacc tcactcctga tttcattgca ggaaaaaagt tagcttgaat
                                                                       360
                                                                       401
atggaccaca aggtaagggc atttgtccat gaatggggct c
      <210> 35
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(401)
      <223> n = A,T,C or G
      <400> 35
cattlettee tactagactg ecceettgat ecaetggeag aaatgatgge accaeettgt
                                                                        60
                                                                       120
cttcaqqtqq tqctccttca ttattccaag gatgcagcat ctctatggtg ccaggtatgg
gggtaaagcc tttggcgccc tttccgcaat ggcacatcag cagtaaaagt ggtaccaata
                                                                       180
gcangaacag aaagggcaaa atcatgancg caattgctgc gggtcccaag cccacatagg
                                                                       240
                                                                       300
aatcatgctg ngcttccctg canccgctgc catgcaagac actnacaaac tgngantgta
                                                                       360
aggacetget tttcaggaca actaaaacce tgattgnetg aaatcaggaa etgaatttca
                                                                       401
cttctcccaa gctttttctc actttggtgc aacancacac t
      <210> 36
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 36
cctgctagaa tcactgccgc tgtgctttcg tggaaatgac agttccttgt tttttttgtt
                                                                        60
                                                                       120
totgtttttg ttttacatta gtcattggac cacagocatt caggaactac cocctgcccc
                                                                       180
acaaaqaaat qaacaqttqt aqqqaqaccc agcagcacct ttcctccaca caccttcatt
ttgaagttcg ggtttttgtg ttaagttaat ctgtacattc tgtttgccat tgttacttgt
                                                                       240
                                                                       300
actatacate tqtatatagt gtacggcaaa agagtattaa tecaetatet etagtgettg
actttaaatc aqtacagtac ctgtacctgc acggtcaccc gctccgtgtg tcgccctata
                                                                       360
ttgagggctc aagctttccc ttgttttttg aaaggggttt a
                                                                       401
      <210> 37
      <211> 401
      <212> DNA
      <213> Homo sapien
```

```
<220>
     <221> misc_feature
      <222> (1)...(401)
      <223> n = A, T, C or G
      <400> 37
cnnctntgna atggantnnt tgnctaaaan ganttgatga tgatgaanat ccctangang
                                                                        60
                                                                       120
antaagcatg ganchtgatc ntttnctnng cactccttta cgacacggaa acangnatca
ncatgatggt accaganacc ttatcaccna cgcgcacnga nctgactnat tccaaagagt
                                                                       180
                                                                       240
tgnggttacg gncatccggt cattgctcgt gcccattgct gcagggctga tnctactggt
                                                                       300
gcttattatg ntggccctga ggatgctcca caatgaatat aagcatgctg catgatcagc
ggcaacanat gctctgccgt ttgcactaca tctttcacgg acacnatntc gaanacgggc
                                                                       360
                                                                       401
acnttgcana gttagacttg gaatgcatgg ngccggncan n
      <210> 38
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 38
                                                                        60
aattggctca ctctctcaag gcaagcactg tctcaaggca gtctcaaggc agagatgaca
cagcaaaaaa cagagggga gaaaaaagtc tattattggc ttgtgattta caaaagccaa
                                                                       120
agtcctttag ataaaaggcc aggagtcgta ccaacataga taccaaatcc aggagaacac
                                                                       180
agaccagcga taagagggac gcttccccat gacccagacc agcctaaagc ccctgtgggg
                                                                       240
gcagccagtg gggagctgtc agaccttgga catggtggtc tttgagaatg ggtctgccct
                                                                       300
                                                                       360
tctctccctg accagttggg atagacacct gactggaatc cttgacactg gcaggtgttt
                                                                       401
ctatgaacag agaggactgt gcctgtcttc ctgaatccca a
      <210> 39
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(401)
      <223> n = A, T, C \text{ or } G
      <400> 39
                                                                        60
tctggtangg agcaattcta ttatttggca ttgcatggct gggttgaatt aaaacaggga
gtgagaacag gtgagtctag aagtccaact ctgaaaagga ccactgtaca tttgaacaca
                                                                        120
cggctgtgtt aaagatgctg ctaatgtcag tcactgggtg cactaaagga tctcttattt
                                                                        180
tatgtaaaac gttgggaatg acaagatana actgatactc tggtaagtta ccctctgaag
                                                                        240
ctacttcttg tgaaatacta atgacagcat catcctgcca agcgaaagag gcaggcataa
                                                                        300
gcaaggacaa attaaaaggg ggtaagagcc ttatcatgat gaggagtctt gttttgacat
                                                                        360
                                                                        401
cttgggaaaa gctgtccata gtgtgaagtc gtcaatttct c
       <210> 40
       <211> 401
       <212> DNA
       <213> Homo sapien
       <400> 40
 tctggtcacc caactcttgt ggaagagggg aattgagatc gagtactgaa tatctggcag
                                                                         60
 agaggctgga atccttcagc cccagagccc agggaccact ccagtagatg cagagagggg
                                                                        120
```

<212> DNA

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cctgcccagg ggtcagggca gtgggtatca ctggtgacat caagaatatc agggctgggg
                                                                        180
aggcatettt gttteetggt geeeteetea aagttgetga caetttgggg aegggaaggg
                                                                        240
gtagaagtag ggctgctcct tttggagctg gagggaatag acctggagac agagttgagg
                                                                        300
cagtcgggct gtccaggttc taagcatcac agcttctgca ctgggctctg aggagattct
                                                                        360
cagccagagg atcccagcct cctcctcct caaatgtcaa g
                                                                        401
      <210> 41
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(401)
      <223> n = A,T,C or G
      <400> 41
ctggactaaa aatgtccact atggggtgca ctctacagtt tttgaaatgc taggaggcag
                                                                        60
aaggggcaga gagtaaaaaa catgacctgg tagaaggaag agaggcaaag gaaactaggt
                                                                       120
ggggaggatc aattagagag gaggcacctg ggatccacct tcttccttan gtcccctcct
                                                                       180
ccatcagcaa aggagcactt ctctaatcat gccctcccga agactggctg ggagaaggtt
                                                                       240
taaaaacaaa aaatccagga gtaagagcct taggtcagtt tgaaattgga gacaaactgt
                                                                       300
ctggcaaagg gtgcganagg gagcttgtgc tcangagtcc agcccgtcca gcctcggqqt
                                                                       360
gtangtttct gaagtgtgcc attggggcct caccttctct g
                                                                       401
      <210> 42
      <211> 310
      <212> DNA
      <213> Homo sapien
      <400> 42
ggttcgacaa atccccaaaa atggcaaatt aagccctgtg acaaaataag ttattggatc
                                                                        60
atacagaaat agcccaaatc tggaaatttt gaattaaaat tgtaatcctg taaaacaagt
                                                                       120
tttggggtga atggatttct ttaataccaa taatatttt aattcccacc acagatggat
                                                                       180
ttgctgaata tgctaatgct gtgaatgaga aaacaatttt ggggtaggta tacccacaag
                                                                       240
taatctgatg acaaaataaa ccacagactg atgtcaaatg gacaaaaaac tgaaaatatg
                                                                       300
ctgtgagaaa
                                                                       310
      <210> 43
      <211> 401
     <212> DNA
     <213> Homo sapien
      <400> 43
aggicacita cacitgigac cagigggggg cagagaccia ccagccgatc cagiciccca
                                                                        60
ctttcatgcc tctgatcatg tgcccaagcc aggagtgcca aaccaaccgc tcaggagggc
                                                                       120
ggctgtatct gcagacacgg ggctccagat tcatcaaatt ccaggagatg aagatgcaag
                                                                       180
aacatagtga tcaggtgcct gtgggaaata tccctcgtag tatcacggtg ctggtagaag
                                                                       240
gagagaacac aaggattgcc cagcctggag accacgtcag cgtcactggt attttcttgc
                                                                       300
caatcctgcg cactgggttc cgacaggtgg tacagggttt actctcagaa acctacctgg
                                                                       360
aagcccatcg gattgtgaag atgaacaaga gtgaggatga t
                                                                       401
     <210> 44
     <211> 401
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<213> Homo sapien

<400> 47

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<400> 44
atccctgtaa gtctattaaa tgtaaataat acatacttta caacttctct tagtcggccc
                                                                         60
ttggcagatt aaatctttgc aaaattccat atgtgctatt gaaaaatgaa ataaaacctc
                                                                        120
agatgtctga attcttattt caaatacagt tatataatta ttttaaatta caatatacaa
                                                                        180
tttctgttaa atacaactgt taagggattc tgagaacaat tataagatta taataatata
                                                                        240
tacaaactaa cttctgaaat gacatgggtt gtttccttcc caccctccta ccctctcaaa
                                                                        300
gagtttttgc atttgctgtt cctggttgca aaaggcaaaa gaaaatctaa aaatagtctg
                                                                        360
                                                                        401
tgtgtgtcca cgacatgctc gctcctttga gaatctcaaa c
      <210> 45
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (401)
      <223> n = A,T,C or G
      <400> 45
                                                                         60
gtgcctgctg cctggcagcc tggccctgcc gctgcctcag gaggcgggag gcatgagtga
gctacagtgg gaacaggctc aggactatct caagagattt tatctctatg actcagaaac
                                                                        120
aaaaaatgcc aacagtttag aagccaaact caaggagatg caaaaaattc tttggcctac
                                                                        180
ctatactgga atggtaaact cccgcgtcat anaaataatg caanaagccc agatgtggag
                                                                        240
tgccagatgt tgcagaatac tcactatttc caaatagccc aaaatggact tccaaagtgg
                                                                        300
teacetacag gategtatea tatactegag acttacegea tattacagtg gategattag
                                                                        360
                                                                        401
tgtcaaaggc tttaaacatg tggggcaaag agatccccct g
       <210> 46
       <211> 401
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(401)
       \langle 223 \rangle n = A,T,C or G
       <400> 46
 gtcagaattg tctttctgaa aggaagcact cggaatcctt ccgaactttc caagtccatc
                                                                          60
 catgattcan agatactgcc ttctctctct ctgggatttt atgtgtttct gatagtgaat
                                                                         120
 tgttgatgta tttgctactt tgcttctttt ctctttcaag acttgatcat tttatatgct
                                                                         180
 gnttggagaa aaaaagaact tttggtagca aggaggtttc aagaaatgat tttggatttt
                                                                         240
 ctgctgcgga atttctcggc acctacctgt agtatggggc acttggtttg gttgcagagt
                                                                         300
 aagaaggtgg aagaatgagc tgtacttggt taagcagttg aaaccttttt tgagcaggat
                                                                         360
                                                                         401
 ctgtaaaagc ataattgaat ttgtttcacc cccgtggatt c
       <210> 47
       <211> 401
        <212> DNA
       <213> Homo sapien
```

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ggtctgcagc aatgcacttc aaccatacat actgcttcca ctagctaata ccaaatgcag
                                                                        60
gttctcagat ccagacaaat ggaggaaaag aacatttatg cttccgtttc agaaagccaa
                                                                       120
                                                                       180
gtcgtagttt tggcccttcc tttctctaaa gtttattccc aaaaacaggt agcattcctg
attgggcaga gaagaggata ttttcagccc acatctgctg caggtatgtc attttctccc
                                                                       240
atcttcactg tgactagtaa agatctcacc acttctcttt ggaatttcca actttgcttg
                                                                       300
tgattgaatg tcacttcgtg aatttgtatt atgtcagatc acttggcatt gctcttccat
                                                                       360
                                                                       401
atgcatcaag ttgccaggca ctaaacccaa tgttcatgaa c
      <210> 48
      <211> 430
      <212> DNA
      <213> Homo sapien
      <400> 48
                                                                        60
acataacttg taaacttttt ctgcttgggg gctgtaacag acagaagagt aaagactaca
aggattttct gaagatgctt caatgaaaat catcatttcc tctttagtca tcccaagtct
                                                                       120
tggtttgaaa aacttgggca tggacttata cagaccttga accaccactg acttatcatt
                                                                       180
gggtggcaga ccttgaaacc aagctctctg tgttacttct gaaagtgcat caattctgat
                                                                       240
ttggctaaga acagaagaca aatactggga tcgtgattct gtgttatact ctagccacag
                                                                       300
                                                                       360
catagoaget tetegaacgg tttetteett ttetacattt aaattgteac tactgagaat
atctatcagt aggtcatgtg acagacetge eeeggggeeg geeegetega tgettgeega
                                                                       420
                                                                       430
atatcatggt
      <210> 49
      <211> 57
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(57)
      <223> n = A,T,C or G
      <400> 49
                                                                        57
ggtattaaca atatcangca ctcattcttc ccctcttatg aaanggatna attttta
      <210> 50
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (327)
      <223> n = A,T,C or G
      <400> 50
gatggnggtn tccacaagan tnaangtncn tattaantan nncttgtaga nccacttnna
                                                                        60
ttaattgnnn tatgnntgnc cttctggtgg ntgtngaagc ttcatatnnt ntttggacat
                                                                       120
cattacacgt cttagctctt tnaagnacaa ctttaatgct atatgaattt tgccattttn
                                                                       180
gctaacactg gtatgctccn ngcatccacc atnccacntg gaattattta ttncnttcat
                                                                       240
attaatnttt tgtttaccaa atctnacttg acccgaacga aactttctgn gtattttang
                                                                       300
                                                                       327
gcccnccat tcttactttt caagcct
```

```
<211> 236
      <212> DNA
      <213> Homo sapien
      <400> 51
cgtctcgaag aagcgctgca ggccgatgat ggactgcacg tctgccttgt cctcagttaa
                                                                         60
cttgttgaat tgcttgaaca tgcggcccac atcctgggca aactcctgtg gggagctgta
                                                                        120
gggaggtgac aactteteet ggaggeggge aeggateagg gteagateea gggtgeeace
                                                                        180
gggctggtcc agggagaagg tggagtcgta gccagacctg cccgggcggc cgctcg
                                                                        236
      <210> 52
      <211> 291
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(291)
      <223> n = A,T,C or G
       <400> 52
ctcacatcct gggtccggct gtagagctgc accatggtgc tgagcgcccc ctccagctcc
                                                                         60
ttgtagatgt aaaggacggc gaaggagctg tagtctgtgt ccacgatgcg cacgtccagg
                                                                        120
tagcccaagg ccgggactct gaagttgtcc ctcggagccc accttcangt actcgggcat
                                                                        180
ccacctggtt acagcentte gneeteggna actecatntg gaetttacag geogeetee
                                                                        240
tetgtgggcc tgatggncct tgcaggacat nggaacacgg gagctcnctt t
                                                                        291
       <210> 53
       <211> 95
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(95)
       <223> n = A,T,C or G
       <400> 53
 gtctgtgcag tttctgacac ttgttgttga acatggntaa atacaatggg tatcgctgan
                                                                          60
                                                                          95
 cactaagttg tanaanttaa caaatgtgct gnttg
       <210> 54
        <211> 66
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(66)
        \langle 223 \rangle n = A,T,C or G
        <400> 54
  cctnaatnat ntnaatggta tcaatnnccc tgaangangg gancggngga agccggnttt
                                                                           60
                                                                           66
  gtccgg
```

```
<210> 55
              <211> 265
              <212> DNA
              <213> Homo sapien
              <220>
              <221> misc feature
              <222> (1)...(265)
              \langle 223 \rangle n = A,T,C or G
              <400> 55
atctttcttc tcagtgcctt ggccntgttg agtctatctg gtaacactgg agctgactcc
                                                                                                                                                                     60
ctgggaagag aggccaaatg ttacaatgaa cttaatggat gcaccaagat atatgaccct
                                                                                                                                                                   120
gtctgtggga ctgatggaaa tacttatccc aatgaatgcc gtgttatgtt tttgaaaatc
                                                                                                                                                                   180
ggaaacgcca gacttctatc ctcattcaaa aatctgggcc ttnctgaaaa ccagggtttt
                                                                                                                                                                   240
naaaatccca ttcnggtcnc cggcg
                                                                                                                                                                   265
              <210> 56
              <211> 420
              <212> DNA
              <213> Homo sapien
              <220>
              <221> misc_feature
              <222> (1)...(420)
              \langle 223 \rangle n = A,T,C or G
              <400> 56
gageggeege eegggeaggt cetegeggtg acitgatggg atttcaaaac ettggttete
                                                                                                                                                                    60
agcaaggccc agatttttga atgangatag aagtctggcg tttccgattt tcaaaacata
                                                                                                                                                                   120
acacgcatte attgggataa gtattteeat eagteecaca gaengggtea tatatettgg
                                                                                                                                                                  180
gtgcatccat taagttcntt tgttaacatt tgggcctctc tttcccangg gaattcagct
                                                                                                                                                                  240
cccagttgtt taccaanatt naactccacc ggggccaaag gcncttgaaa aaaaaaanaa
                                                                                                                                                                  300
ttccttgttt accttccttg ggcttnaagt tctggcqtcc aaaaqttcaa tttgaaaact
                                                                                                                                                                  360
gcaccgcact taccacgtct cttcnagaan cctggggaca cctcggccgc gaccacgcta
                                                                                                                                                                  420
              <210> 57
              <211> 170
              <212> DNA
              <213> Homo sapien
              <400> 57
gaagcggagt tgcagcgcct ggtggccgcc gagcagcaga aggcgcagtt tactgcacag
                                                                                                                                                                    60
gtgcatcact tcatggagtt atgttgggat aaatgtgtgg agaagccagg gaatcgccta
                                                                                                                                                                  120
gactotogoa otgaaaattg tototooaga cotoggoogo qaccacqota
                                                                                                                                                                  170
              <210> 58
             <211> 193
              <212> DNA
             <213> Homo sapien
              <400> 58
attiticaging changes of the second of the se
                                                                                                                                                                    60
ctccatgaag tgatgcacct gtgcagtaaa ctgcgccttc tgctgctcgg cggccaccag
                                                                                                                                                                  120
gegetgeaac teegetteat eggettegee eageteegee attgttegee acetgeeegg
                                                                                                                                                                  180
```

gcggccgctc gaa	193
<210> 59 <211> 229 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 59  cgcaactctc gagcatttat atacaatagc aaatcatcca gtgtgttgta cagtctataa tactccaaca gtctcccatc tgtattcaat ggcgccaccc aatacagtcc tttgtttgga tgctggggag agtaatccct accccaagca ccatatagat aagaaaaccc tctccagttg agctgaacca cagacggttt gctgatacct gcccgggcgg ccgctcgaa</pre>	60 120 180 229
.<210> 60 <211> 340 <212> DNA <213> Homo sapien	
tegageggee geegggeag gteetetaaa gateaaaaca eeeetgtegt eeaceteet eecacteeag ggaagetgtg gteatggtgg tgtggtgaac ateageaaac egtetgtggt teageteaac tggagagggt tttettatet atatggtget tggggtaggg attactetee eeageateea aacaaaggae tgtattgggt ggegeeattg aatacagatg ggaaactgtt ggagtattat aaactggtae aacacactgg atgatttget attgtatata aatgetegag aattgeggat eacetatgga eeteggeege gaeeaegetg	.60 120 180 240 300 340
<210> 61 <211> 179 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(179) <223> n = A,T,C or G	
<400> 61 tttttgtgac ggacgnttgg agtacatgtc ccaggatcac atccagcagc tagagtggct gggacaagct ggcggnggcc aagcactgtt gaaacnatag gggtctgggn gnactcgggt tnaagtggtt ggtccgantn ttnataacct tgtcngaacc nancatctcg gttgncang	60 120 179
<210> 62 <211> 78 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(78) <223> n = A,T,C or G	
<400> 62 agggcgttcg taacgggaat gccgaagcgt gggaaaaagg gagcggtggc nggaagacgg ggatgagctt angacaga	60 78

```
<210> 63
      <211> 410
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(410)
      <223> n = A, T, C \text{ or } G
      <400> 63
cccagttact tggggaggct gaggcaggga gaatcctttg aacccggngg gtgggaggtt
                                                                      60
gcagtgagcc cgagatagca ccattgcact tccancatgg ggtggacaga gtgagactct
                                                                     120
180
tntcccattt caagteetga aaatagagga teagaaatgt tgaggaatte tttaggatag
                                                                     240
aaagggagat gggattttac ttatggggaa agaccgcaaa taaagactgn aacttaacca
                                                                     300
cattccccaa gtgnaaggtg ttacccaaga agtaggaacc cttttggctn ttaccttacc
                                                                     360
ttccngaaaa aaacttattn cttaaaatgg aaacccttaa agcccgggca
                                                                     410
      <210> 64
      <211> 199
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(199)
      <223> n = A, T, C \text{ or } G
      <400> 64
cttgttctca aaaaggtcaa agggagcccg acgaggaata aatagcaatg ccctgaattc
                                                                      60
caactgacct tctacagaaa agtgcttgac tgccaagtgg tcttcccagt cattagtgag
                                                                     120
gctcttgtag aattctccat actcctcttg ggngangnca tnagggtttn nggcccaaat
                                                                     180
aggntgggcc tngttaagt
                                                                     199
      <210> 65
      <211> 125
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc_feature
     <222> (1)...(125)
     <223> n = A, T, C or G
     <400> 65
ageggtacag ttetgteetg geateateat teattgtagt atggteaata ggtgeeatga
                                                                     60
aactcagtag cttgctaagg acatgaaacc gaagtttcct gcctttgctg gcctngtngn
                                                                    120
gggta
                                                                     125
     <210> 66
     <211> 204
     <212> DNA
     <213> Homo sapien
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<400> 66
attcagaatt ctggcatcgg tatttctata aagtccatca gttagagcag gagcaggccc
                                                                         60
ggagggacgc cctgaagcag cgggcggaac agagcatctc tgaagagccc ggctgggagg
                                                                        120
aggaggaaga ggagctcatg ggcatttcac ccatatctcc aaaagaggca aaggttcctg
                                                                        180
                                                                        204
tggacctcgg ccgcgaccac gcta
      <210> 67
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (383)
      <223> n = A,T,C or G
      <400> 67
tcagggcctc caggcagcca gttttgcagg anattcagca cctagngtct tcctgcctna
                                                                         60
cgctcccaag aacctgctcc tgcaggggga acatcagaac tcgtccttga tgtcaaaatg
                                                                        120
gggctggtct tnaggcttga agtccaggtt agggctgcca tcctcattga gaattctccg
                                                                        180
ggcagtgtan ccgacgatgg ggtatttggc tttgtacact ttggtgaaaa cctnatccag
                                                                        240
ggcctccagt tccttggccg tganacccgt antgtcatgg gtgaggtctg caggatccaa
                                                                        300
ggacatettg getacecete tagtggagte etteceegte aaggeattgt aaggggetee
                                                                        360
                                                                        383
tcgtccataa aactcctttt cgg
      <210> 68
      <211> 99
      <212> DNA
      <213> Homo sapien
       <400> 68
                                                                         60
tcacatctcc ttttttttt aactttttca aatttttgtg ttaaatagaa ggctaaaggg
                                                                         99
ttagatttaa gtttctgcta cattgaccct atttaccta
       <210> 69
       <211> 37
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(37)
       \langle 223 \rangle n = A,T,C or G
       <400> 69
                                                                         37
 gagaaggacn tacggncctg ntantanang aatctcc
       <210> 70
       <211> 222
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(222)
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<223> n = A,T,C or G
      <400> 70
gtgggtcatt tttgctgtca ccagcaacgt tgccacgacg aacatccttg acagacacat
                                                                          60
tottgacatt gaageecaca ttgteeccag gaagagette acteaaaget teatggegea
                                                                         120
tttcgacaga ttttacttcc gttgtaacgt tgactggagc aaaggtgacc accataccgg
                                                                         180
gtttgagaac acccantcac ctgccccggg cggccgctcg aa
                                                                         222
      <210> 71
      <211> 428
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(428)
      \langle 223 \rangle n = A,T,C or G
      <400> 71
caggagtatt ttgtagaaaa gccagaagag cattagtaga tgtatggaaa tatacggtag
                                                                          60
ggcacacgct gacagtactt ttcccaagcc acgccgtatt tcttcttaca gtggtactcq
                                                                         120
tcacgagctt ctcggtggac aagcaacatg gtgaaataaa ttatgtagaa ataaggcaga
                                                                         180
atgtggttaa aaccacatgg gagggaccac gccaaggcca tgatgagatc acccaagtaa
                                                                         240
ttggggtggc gaacaaagcc ccaccatcca gaaactagaa naatttttcc cqttqaaata
                                                                         300
tgaatggntt ttaaatgtgc aagctttgga tcactgggaa ttttcccqaa tqcctttttc
                                                                         360
tganaattgc acctinggaa gantccttac cccaagnitc agaccattat tinaaaaqcn
                                                                         420
ttggaact
                                                                         428
      <210> 72
      <211> 264
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(264)
      <223> n = A, T, C or G
      <400> 72
gaataaagag cttactggaa tccagcaggg ttttctgccc aaggatttgc aagctgaagc
                                                                         60
tctctgcaaa cttgatagga gagtaaaaag ccacaataga gcagtttatg aagatcttgg
                                                                        120
aggagattga cacacttgat cctgccagaa aatttcaaag acagtagatt gaaaaggaaa
                                                                        180
ggctttggta aaaaaaggtt caggcattcc tagccgantg tgacacagtq qaqcanaaca
                                                                        240
tctgcangag actgancggc tgca
                                                                        264
      <210> 73
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(442)
      \langle 223 \rangle n = A,T,C or G
```

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<400> 73
ggcgaatccg gcgggtatca gagccatcag aaccgccacc atgacggtgg gcaagagcag
                                                                        60
caagatgctg cagcatattg attacaggat gaggtgcatc ctgcaggacg gccggatctt
                                                                        120
cattggcacc ttcaaggctt ttgacaagca catgaatttg atcctctgtg actgtgatga
                                                                        180
qttcagaaag atcaagccaa agaacttcaa acaagcagaa agggaagaga agcgagtcct
                                                                        240
eggtetggng etgetgeeaa gggagaatet ggteteaatg aengtagaag gaeettette
                                                                        300
caaagatact ggnattgctc gagttccact tgctggaact tcccggggcc caaggatcgc
                                                                        360
aaggettetg geaaaagaaa teeanaettn ggeegggaee aeetaaneea atteacaeae
                                                                        420
                                                                        442
tggcggccgt actagtggat cc
      <210> 74
      <211> 337
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(337)
      \langle 223 \rangle n = A,T,C or G
      <400> 74
ggtagcagcg tctccagagc ctgatctggg gtcccagata cccaggcagc agcagccctg
                                                                         60
gaggtaaagg gcaagctccc caatgtgagg ggagacccca ttcctggtca gccaggcttt
                                                                        120
cagaggagat agcaggtcga gggagccaac gaagaagaga ctgccancag gggaaggact
                                                                        180
gtcccgccaa ggacagaact gattcagggg ggtcaatgct cctctagaga agagccacac
                                                                        240
agaactgggg ggtccaggaa ccatgaanct tggctgtggt ctaaggagcc aggaatctgg
                                                                        300
                                                                        337
acagtgttct gggtcatacc aggattctgg aattgta
       <210> 75
       <211> 588
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(588)
       <223> n = A, T, C or G
       <400> 75
 catgatgagt totgagctac ggaggaaccc toatttootc aaaagtaatt tatttttaca
                                                                         60
 gcttctggtt tcacatgaaa ttgtttgcgc tactgagact gttactacaa actttttaag
                                                                         120
 acatgaaaag gcgtaatgaa aaccatcccg tccccattcc tcctcctct tgagggactg
                                                                         180
 gagggaagee gtgettetga ggaacaacte taattagtae aettgtgttt gtagatttae
                                                                         240
 actttgtatt atgtattaac atggcgtgtt tatttttgta tttttctctg gttgggagta
                                                                         300
 tgatatgaag gatcaagatc ctcaactcac acatgtagac aaacattagc tctttactct
                                                                         360
 ttctcaaccc cttttatgat tttaataatt ctcacttaac taattttgta agcctgagat
                                                                         420
 caataagaaa tgttcaggag agangaaaga aaaaaaatat atgttcccca tttatattta
                                                                         480
 gagagagacc cttantcttg cctgcaaaaa gtccaccttt catagtagta ngggccacat
                                                                         540
                                                                         588
 attacattca gttgctatag gncagcactg aactgcatta cctgggca
       <210> 76
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<211> 196

<212> DNA

<213> Homo sapien

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<400> 76
geggtateae ageetggeee eeatgtaeta teggggggee eaggetgeea tegtggteta
                                                                          60
tgacatcacc aacacagata catttgcacg ggccaagaac tgggtgaagg agctacagag
                                                                         120
geaggecage eccaacateg teattgeact egegggtaac aaggeagace tggacetgee
                                                                         180
cgggcggccg ctcgaa
                                                                         196
      <210> 77
      <211> 458
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(458)
      \langle 223 \rangle n = A,T,C or G.
      <400> 77
agtagagatg gggtttcact gtgttaacca ggatggtctt gatctcctgg cctcgtgatc
                                                                          60
tgcccgcctc ggcctcccaa agtgttggga ttacaggcgt qaaccaccqc acccqqccaq
                                                                         120
aaatgttagt ttttccctat tctctctcct ttttcctatt atatacttgg tcaaccagac
                                                                         180
agccatccta ccccanaatg gtaatgcctc ttcattcctc atatgaggga ataaaagaga
                                                                         240
aaaaagcttt tggaaaacat ccacttatct aatcatccca aatatgtaat caaaagtata
                                                                         300
caactcatgt gaagaataca ctggtaaaat gttantatag gccaaggtat cttgaattcc
                                                                         360
tatatagaaa gctggtaaat gcccttttgg ctggaaccgc catcttccnn taattcnccc
                                                                         420
aaaatgacca aacacaaagg gnaagangan aagccccc
                                                                         458
      <210> 78
      <211> 464
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(464)
      <223> n = A, T, C \text{ or } G
      <400> 78
tccgcaaatt tcctgccggc aaggtcccag catttgaggg tgatgatgga ttctgtgtgt
                                                                         60
ttgagagcaa cgccattgcc tactatgtga gcaatgagga gctgcgggga agtactccag
                                                                         120
aggcagcagc ccaggtggtg cagtgggtga gctttgctga ttccgatata gtgcccccag
                                                                         180
ccagtacctg ggtgttcccc accttgggca tcatgcacca caacaaacag qccactgaga
                                                                        240
atgcaaagga ggaagtgagg cgaattctgg ggctgctgga tqcttacttq aaqacqaqqa
                                                                         300
cttttctggt gggcgaacga gtgacattgg ctgacatcac agttgtctgc accctgttgt
                                                                        360
ggctctataa gcaggntcta gaaccttctt ttcgcangac cttcggccgg accacgctta
                                                                        420
acccaaattc cacacattg enggeegtac taanggaatc ccac
                                                                        464
      <210> 79
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(380)
      <223> n = A, T, C \text{ or } G
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<400> 79
ctgtatgacc agtttttcca tctccttcac ttctaccttg atcagctcga agtccagttc
                                                                        60
agtgtaagaa atggtateet tetecatgat gteaattegg acagttaggt ttaacagttt
                                                                       120
cttttcatac acactaatta attggacata ttccctcact ttanaaagtt ctttctcaaa
                                                                       180
cttctganaa aagaacatga actgtgaatt ccaagcgttc ccactctgtc cacgggaaaa
                                                                       240
ggtggtgtct ggcagggaaa cagaacactg gcaggtccac ggtcatccac ggagccggtg
                                                                       300
aaattgggaa aacaactggg acacagaacc tccgctgcct aagctgcggn tgggagcttg
                                                                       360
                                                                       380
gaacccgacc tggaactgga
      <210> 80
      <211> 360
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (360)
      <223> n = A,T,C or G
       <400> 80
tegageggee geeegggeag gteeteagag agetgtttgt tnegettett caaaaactee
                                                                         60
tattctccac ttctgctaaa ggactggatg acatcaattg tgatagcaat atttgtgggt
                                                                        120
gttctgtcan ncancatcgc actcctgaac aaagtagatg ttggattgga tcagtctctt
                                                                        180
tecacecaga tgaetectan atggtggatn attteaaate cateanteag tacetgeatg
                                                                        240
 cgnggtccgc ctgtgtnctt tgtcctgcag gangggcnct actacacttc ttccnagggg
                                                                        300
 canaacatgg tgtgcngcgg ccatgggctg gcaacantga ttcnctgctg cacccanatn
                                                                        360
       <210> 81
       <211> 440
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (440)
       <223> n = A,T,C \text{ or } G
       <400> 81
 acgtggtccg gcgagtctga cctgcagata tgaactcctt gggaaaccta cattctgcct
                                                                          60
 cagacatact gggggcaaat ggctttaaaa gtctggctca gggagccaag attacagaaa
                                                                         120
 nccgttgagt cnccatacat ggacactgac aaaggaactg aagatatcca aacaagccct
                                                                         180
 cetggteeeg ngcetgeata aagateggga neggaaeggt acengaegte tgtggteagg
                                                                         240
 ggttgtggaa aattggaaaa aaccagtcct gcccacattg acagggaagc ctcaacggaa
                                                                         300
 attgaacaga tngtcttatc accagtctcc cctcctggat cntgtctcgg ctcnggggan
                                                                         360
 tcagtgatca gtcctttcag gtggaagaag caaagaagat caacaanaag cngatcctct
                                                                         420
                                                                         440
  cacctgntac cagcatatgg
        <210> 82
        <211> 264
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc feature
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<222> (1)...(264)
      <223> n = A, T, C \text{ or } G
      <400> 82
agcqtqqtcq cqqccqanqt cctqacattc ctgccttctt atattaatta tacnaataaa
                                                                         60
acaaaatagt gttgaagtgt tggagcggcg aaaatttttg gggggtggta tggacagaga
                                                                        120
                                                                        180
atqqqcqatn ttctcangqc tgcttcaaqt qgqattgggg cngcgtggga tcatncagtg
gganagattn cnctgaccgg antctnttgg tanggatnat cttgtgggga tgtgcaagag
                                                                        240
                                                                        264
ncattcgtct cctgaatgan tggt
      <210> 83
      <211> 410
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (410)
      <223> n = A, T, C or G
      <400> 83
                                                                         60
ancettagted edgecangt ceacagttqt qqqaqaqeca qecattgtgg gggcagetee
acaggtaaga ctcgtgtcct gagcagcgca catcatccag gacaatgggt cctgagccct
                                                                        120
gaccaaaccg ggcatttcct ggggctgaca tggcccagcc acagcccant tgcctgcaga
                                                                        180
cgaaattggc atcattggtg tcccagtant catcacacac ggtgccccag gaacctccgg
                                                                        240
tatanqaact ccacteggee tenanacetg tegeetecat teencageet cagggggcaa
                                                                        300
actgggattc agatcettet gtgggtacag gtggtgatat cetgacagge caactttetg
                                                                        360
                                                                        410
gcctgagtgt tgactgangc tgggcagacc tgcccgggcg gccgctcgaa
      <210> 84
      <211> 320
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(320)
      <223> n = A, T, C \text{ or } G
      <400> 84
                                                                         60
togaacggcc gcccgggcag gtctgcccca ggtgtatcca tttgccgccg atctctatca
naaggagetg getaceetge nnegaegaan teetgaanat aateteacee neeeagatet
                                                                        120
ctctqtcqca atggagatgt cgtcatcggt ggncctgatc acagggcatt ggactcagag
                                                                        180
anangtnanc acagtgtnga agcgattgan nnagttcagt tgctggtctt acccgatntt
                                                                        240
                                                                        300
qqaaqqaaqq aaaacqtqtt angacqtatc tcgatgnant tgaccaaanc tgaangctnc
agggggcatc gcaaaganan
                                                                        320
      <210> 85
      <211> 218
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(218)
```

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<223> n = A,T,C or G<400> 85 tegageggee geeegggeag gtetgetgee egtgetggtg ceattgeece atgtgaagte 60 actgtgccag cccagaacac tggtctcggg cccgagaaga ctcctttctc caggctntan 120 180 gtatcaccac taaaatctcc aggggcacca tnganatcct gggtgtccgc aatgttgcca 218 atgtctgtcc gcnnattggc tacccaactg ttgcatca <210> 86 <211> 283 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(283) <223> n = A, T, C or G<400> 86 tcgacttctt gtgaaggttt tgganaaata tgtatcagtt cgttttattt gggtattcaa 60 taatateett ggtgataatg etgacteeat ggettetgae eecaaaaatt gaeeetgetg 120 ccactggttg tagccctgag attgattttt gtagccacga ttgtttcctc gtcctctgaa 180 gtnctggttg tanttccctc tgtngggcat tcccctctgt tgtanttccc tctgtttgan 240 283 taactaccac ggccaggaaa aacaggggca cgaaggtatg gat <210> 87 <211> 179 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(179) <223> n = A, T, C or G<400> 87 agcgtggtcc cggccgatgt ctttctgtgt aagtgcataa cactccacat acttgacatc 60 cttcangtca cgggccagct nttcagcant ctctggagtg ataggctact gtntgttctn 120 ggcaagtgtc tcaanaatac aggggtcntc tctgagatga ntttcagtcc cgaaccctc 179 <210> 88 <211> 512 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(512) <223> n = A, T, C or G<400> 88 tegageggee geeegggeag gteetanean agaateacea aatttatgga gagttaacag 60 gggtttaaca ggaangaagt gcctttagta agttctcaag ccagangctg gaggcagcag 120

ctaaatcaga ggacaggatc ctcagtgaaa gtgagccatt cggggtggca tgtcactcca

ggaataagca caacttanaa acaaatgatt tcgtangata gcacagtgac attggtgcac

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```
ttgtgaacct gaggccactg tgtcaaactg tgcactggtt gtgaataggg aganccaaaa
                                                                         300
attatgtcct actgggtaat gagctttcaa tgggctcgat cctctcacnc tgaaaqctct
                                                                         360
gtagagcagc tcagaaccac aaccactccc aacattgacc cttctggggg tactqtctqt
                                                                         420
ggcacccaca ggaaggagct ggagatcccc attaggactg tccacccaca cttgaagcca
                                                                         480
caaaactgca cctcggccgc gaccaccgct ta
                                                                         512
      <210> 89
      <211> 358
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(358)
      \langle 223 \rangle n = A,T,C or G
      <400> 89
tegageggge egecegggea ggtetgeeag tececatece agacattett tgeatetaag
                                                                         60
ctgangtetg aactgagtgg ggtgggetgg tgtttccatc ctcacaactc cagtgagccg
                                                                        120
ggtgtggccg tggcctgcgt ctctctggcg gttagtgatg ttggcatcat ccaccttttt
                                                                        180
caaaacaaaa gcactggact gaagaanaat cccnccctgt ntccacccag tccatggttt
                                                                        240
ttaataaaag ggttatnnaa gttgancaag ncatcaccac acacaancct aagaacnttt
                                                                        300
ttcatcnntc cccaaaacaa accencacee tgggaactee gggegegaac caegeeta
                                                                        358
      <210> 90
      <211> 250
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(250)
      <223> n = A, T, C or G
      <400> 90
cgagcggccg cccgggcagg tctggatggg gagacggact ggaactgcgg cttcccgtgg
                                                                         60
cetgeacgea caaggeteec caeggeegee gacettette agattegate gtatgtgtae
                                                                        120
gcacnaagag ccaaatattg acattcacaa cttcgtggga atnttacccc anaagactgc
                                                                        180
gaccccccga tcaggcgana gcctgagcat agaagaacac cgctgtgggc ttggcactgt
                                                                        240
gggncccatc
                                                                        250
      <210> 91
      <211> 133
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(133)
      \langle 223 \rangle n = A,T,C or G
      <400> 91
tcgagcggcc gnccgggcag gtcccgggtg gttgtttgcc gaaatgggca agttcntnaa
                                                                         60
ncctgggaag gtggtgcntg tnctggctgg acgctactcc ggacgcnaag ctgtcntcgt
                                                                        120
gangancatt gat
                                                                        133
```

```
<210> 92
     <211> 232
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
      <222> (1)...(232)
      \langle 223 \rangle n = A,T,C or G
      <400> 92
agcgtggtcg cggccgangt ctgtcacttt gcgggggtag cggtcaattc cagccaccag
                                                                         60
agcatggctg taggggcgat ctgaggtgcc atcatcaatg ttcttcacga tgacaagctt
                                                                        120
tgcgtccgga gtagcgtcca gccaggacaa gcaccacctt cccacgtntt cangaactng
                                                                        180
                                                                        232
cccatttcgg cataaccacc cgggacctgc ccgggcggnc gctcgaaaag cc
      <210> 93
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      \langle 223 \rangle n = A,T,C or G
      <400> 93
                                                                         60
agcgtgggtc gcggccgang tctgtangct caccggccag agaagaccac tgtgagcatt
ttgccgtata tcctgccctg ccatttgttc actttttaaa ctaaaatagg aacatccgac
                                                                        120
acacaccgtt tgcatcgtct tctcccttga tattttaagc attttcccat gtcgtgagtt
                                                                        180
tctcagaaac atgttttaa caattgtact atttagtcat ngtccattta ctataattta
                                                                        240
tctgaccatt tccctactgt taaaatactt aagacggttt ctgatttttc cactatttaa
                                                                        300
ataatgctgt gatgaatatc tttaaaatct tctgatttct tacttttttc ccccttagat
                                                                        360
gcctggaagt ggtattttga ggtgaaagag tttgttcatt ttgaanatat ttctgtctct
                                                                        420
ctctcgacct gatgtgtana cgctcacttc cagttagcag aaccacctta gtttgtgtct
                                                                        480
      <210> 94
      <211> 472
      <212> DNA
      <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(472)
       <223> n = A, T, C or G
       <400> 94
tcgagcggnc gcccgggcag ggtctgatgt cantcacaac ttgaagggat gccaatgatg
                                                                          60
taccaateen atgtgaaate teteetetta teteetatge tgganaaggg attacaaagt
                                                                         120
 tatgtggcng ataannaatt ccatgcacct ctantcatcg atgagaatgg agttcatgan
                                                                         180
                                                                         240
 ctggtgaacn atggtatctg aacccgatac cangttttgt ttgccacgat angantagct
 tttatttttg atagaccaac tgtgaaccta ccacacgtct tggacnactg anntctaact
                                                                         300
 atconcaggg ttttattttg cttgttgaac tcttncagct nttgcaaact tcccaagatc
                                                                         360
 canatgactg antitcagat agcattita tgattcccan cicattgaag gictiainta
                                                                         420
```

```
tntcnttttt tccaagccaa ggagaccatt ggacctcggc cgcgaccacc tn
                                                                        472
       <210> 95
       <211> 309
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (309)
      <223> n = A,T,C or G
      <400> 95
tcgagcggcc gcccgggcag agtgtcgagc cagcgtcgcc gcgatggtgt tgttggagag
                                                                         60
cgagcagttc ctgacggaac tgaccagact tttccanaag tgccggacgt cgggcancgt
                                                                        120
ctatatcacc ttgaagaant atgacggtcg aaccaaaccc attccaaaga aangtactgt
                                                                        180
gganggettt ganceegeag acaacnagtg tetgttaaga actacegatn ggaaanaana
                                                                        240
anatcagcac tgtgggtgag ctccnaggga agttaataan tttcggatgg gcttattcna
                                                                        300
acctcctta
                                                                        309
      <210> 96
      <211> 371
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(371)
      <223> n = A, T, C \text{ or } G
      <400> 96
tcgagcggcc gcccgggcag gtccaccact cacctactcc ccgtctctat agatttgcct
                                                                         60
gttctgggca gttctcagca atggaatcct actgtgtatc tttttgtgac tggttcttta
                                                                        120
actcagcatc acattttcaa ggttcatcca tgctgcagcc tggctccgta ctggtgacag
                                                                        180
tacttcattt ctctctccct tttgttcaga ccaaggtctc cctctgtccc caaggctaaa
                                                                        240
gtgcagttgg tgtgatcatg gctcactgca gcctcaaact cctggactca aacagtcctc
                                                                        300
ccatctcagc ctcccaaagt gctgatntta taagttgcaa gccctgcacc cagcctgtat
                                                                        360
ctccagtttg t
                                                                        371
      <210> 97
      <211> 430
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(430)
      <223> n = A,T,C or G
      <400> 97
toganoggoo goooggoog gtttnttttn tttnttttt nnnngntagt atttaaagan
                                                                        60
atttattaaa tcatcttatc accaaaatgg aaacatnttc caactagaaa catgcnacca
                                                                       120
tcatcttccc cagtccagtc ncaangtcca atattttnct tgcctctgca gataaaaagt
                                                                       180
tennattttt atacceacte ttacteccee ceaaaatttt aattengtee tnecetaaaa
                                                                       240
ttncnccggg taacaantta ccaaaatggc naaccaatta ttttaaanaa aagttgcncn
                                                                       300
```

ttnaaaangg aaactttntg gcaanttanc ctcttttccc ttcccacccc ccantttaag gggaaaacaa tggcactttg ctcttgcttn aacccaaaat tgtcttccaa aaactattaa aaatgttnaa	360 420 430
<210> 98 <211> 307 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(307) <223> n = A,T,C or G	
<pre>&lt;400&gt; 98 tcnaacggcc gcccnggcnn gtctngcngc acctgtgcct cancegtcga tacctggtcg attgggacan ggaanacaat ntggttttca gggaggccac anatttggag aaacggatga attctccttt attccgaant cagctccttg gtctccgtag anggtgatct tgaaattctc ctgttttgaa aactttcttg aanaaacctt acctgctggt tgtatttggt ctcccactcg gacaagtact cgttatccnn ggtactctta atgtgcccac gtnaactccc cgggntggca actggaa</pre>	60 120 180 240 300 307
<210> 99 <211> 207 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(207) <223> n = A,T,C or G	
<pre>&lt;400&gt; 99 gtccnggacc gatgttgcna aganntttct tggtccanta ggttcnaaaa aatgataanc naggtntanc acgtgaagat ntntatanag tcttantnaa aacncntaga tctgnatgac gataantcga anacnggggg aggggntgag gngaggtggn gtganggaag anntgttgat aaaagannna gntgataaga anngagc</pre>	60 120 180 207
<210> 100 <211> 200 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(200) <223> n = A,T,C or G	
<400> 100 acntnnacta gaantaacag ncnttctang aacactacca tctgtnttca catgaaatgc cacacacata naaactccaa catcaatttc attgcacaga ctgactgtaa ttaattttgt cacaggaatc tatggactga atctaatgcn nccccaaatg ttgttngttt gcaatntcaa acatnnttat tccancagat	60 120 180 200

```
<211> 51
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(51)
      <223> n = A, T, C \text{ or } G
      <400> 101
tcgagcggcc gcccgggcag gtctgaccag tgganaaatg cccagttatt g
                                                                           51
      <210> 102
      <211> 385
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(385)
      \langle 223 \rangle n = A,T,C or G
      <400> 102
aacgtggtcg cggccgaagt ccatggtgct gggattaatc cactgtgacn gtgactctga
                                                                          60
gttgagttgt ttttcaatct tctccaagcc tgtggactca tcctccacat ccttgggtag
                                                                         120
taggatgaac atgctgaaga tgctnatttt gaaaaggaac tctatgaatc ttacaattga
                                                                         180
atactgtcaa tgtttcccca tnacagaacg tggnccccca aggttccatc atctgcactg
                                                                         240
ggtttgggtg ttctgtcttg gttgactctt gaaaagggac atttctttt gttttcttga
                                                                         300
attcanggaa attttcttca tccactttgc ccacaaaagt taggcagcat ttaaccccca
                                                                         360
anggattttg ggtctgggtc cttcc
                                                                         385
      <210> 103
      <211> 189
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(189)
      <223> n = A, T, C or G
      <400> 103
agegtggteg eggeegaagt etgeageetg ggaetgaeeg ggaagetetg attatttaee
                                                                          60
caccacaggt angitgigtt cigaatcica agitcacagg traaggctac agcatccica
                                                                         120
tcctccacgg ggttggantt gttgctggtg atgaanggtt tggggtggct ctgcataact
                                                                         180
gttgatctc
                                                                         189
      <210> 104
      <211> 181
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(181)
      <223> n = A, T, C \text{ or } G
```

```
<400> 104
                                                                         60
tegageggee geoegggeag gteeaggtet ceaceaange accaeegtgg gaagetggta
attgatgccc accttgaagc cnntggggca ccatccncca actggatgct gcgcttggtt
                                                                        120
ttgatggtgg caatggcaca ttgactcttt tgggaaccac ttcaccacgg tacaacaggc
                                                                        180
                                                                        181
a
      <210> 105
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(327)
      <223> n = A, T, C \text{ or } G
      <400> 105
tcgagcggcc gcccgggcag gtcttctgtg gagtctgcgt gggcatcgtg ggcagtgggg
                                                                        60
ctgccctggc cgatgctcan aaccccagcc tctttgtaaa gattctcatc gtgganatct
                                                                        120
ttggcagcgc cattggcctc tttggggtca tcgtcgcaat tcttcanacc tccanaatga
                                                                        180
anatgggtga ctanataata tgtgtgggtn gggccgtgcc tcacttttat ttattgctgg
                                                                        240
                                                                        300
ttttcctggg acagaactcg ggcgcgaaca cgcttanccg aattccaaca cactggcggg
                                                                        327
cgttactagt ggatccgagc tcggtac
      <210> 106
      <211> 268
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(268)
      <223> n = A,T,C or G
      <400> 106
                                                                         60
agegtggteg eggeegangt etggegtgtg ceacateggt eccaectege tttacaaaac
                                                                        120
agtcctgaac ttnatctaat aaaattattg tacacnacat ttacattaga aaaaganagc
tgggtgtang aaaccgggcc tggtgttccc tttaagcgaa ngtggctcca cagttggggc
                                                                        180
atcgtcgctt cctcnaagca aaaacgccaa tgaaccccna agggggaaaa aggaatgaag
                                                                        240
                                                                        268
gaactgnccn gggangnccg ctccgaaa
      <210> 107
      <211> 353
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(353)
      \langle 223 \rangle n = A,T,C or G
       <400> 107
                                                                         60
tegageggee geeegggeag gtggeeagge catgttatgg gateteaacg aaggeaaaca
cctttacacn ctagatggtg gggacatcat caacgccctg tgcttcagcc ctaaccgcta
                                                                        120
```

```
ctggctgtgt gctgccgcag gccccagcat caagatctgg gatttanagg gaaagatcnt
                                                                        180
tgtnnatgaa ctgaanchta aattatcagt tccannacca ngcaaaaacc accengtgca
                                                                        240
ctccctggcc tggtctgctg atgggacctc gggcgcgaac acgctnancc caattccanc
                                                                        300
acactgggcg gncgttacta ntggatccga actcnggtac caancttggc gtt
                                                                        353
      <210> 108
      <211> 360
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(360)
      <223> n = A,T,C or G
      <400> 108
agogtggtog oggoogaagt ootggootca catgacootg otcoagcaac ttgaacagga
                                                                         60
naagcagcag ctacatcctt aaggtccgga aagttagatg aagatttgga tcctgcattg
                                                                        120
ncctgcctcc cacctatctc tcccnaatta taaacagcct ccttgggaag cagcagaatt
                                                                        180
taaaaaactct cccnctgccc tnttgaacta cacaccnacc gggaaaacct ttttcanaat
                                                                        240
ggcacaaaaa tncnagggaa tgcatttcca tgaangaana aactgggtta cccaaaatta
                                                                        300
ttgggttggg gaaatccngg gggggttttn aaaaaagggc aanccnccaa anaaaaaaac
                                                                        360
      <210> 109
      <211> 101
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc feature
      <222> (1)...(101)
      \langle 223 \rangle n = A,T,C or G
      <400> 109
atcgtggtcn cggccgaagt cctgtgtcct ggatgggccg tgtgcancga atccgttggc
                                                                         60
gactcctaac taccaanaaa angactctcg gaagaaattt c
                                                                        101
      <210> 110
      <211> 300
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (300)
      <223> n = A, T, C \text{ or } G
      <400> 110
ccanggaaac ccagagtcac atgagatagg gtggctttcg ggacaggggg tcagangaat
                                                                         60
ggtacatgga tctcagcccc tgatggacac ggaacaggtg tggtcagaac tcccangatt
                                                                        120
ctgcatccan gatccagtct ctatagaagt tatggatcat tccttcattt cattcccccc
                                                                        180
ttcatqaaaa aacttctqaa caagcctttt ttctcacttt ggggccctgt ttggcncaag
                                                                        240
qtnttnantt qqqqaaaaaa aaacaaatcc nttccnttan ccctccgtgg ggaatgacct
                                                                        300
```

<213> Homo sapien

```
<211> 366
     <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
      <222> (1)...(366)
      <223> n = A, T, C or G
      <400> 111
cgagcggccg cccgggcagg tccttgtgtt gccatctgtt ancattgatt tctggaatgg
                                                                     60
                                                                     120
aacanctttc tcaaagtttg gtcttgctan tcatgaagtc atgtcagtgt cttaagtcac
tgctgctcac ttccttaccc agggaatata ctgcataagt ttctgaacac ctgttttcan
                                                                    180
tattcactgt tcctctcctg cccaaaattg gaagggacct catttaaaaa tcaaatttga
                                                                    240
                                                                    300
atcctgaaan aaaaacngga aatntttctc ttggaatttg gaatagaatt attcanttga
ataacatqtt ttttcccctt gccttgctct tcncaanaac atctggacct cggccgcgac
                                                                    360
                                                                    366
acctta
      <210> 112
      <211> 405
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(405)
      <223> n = A, T, C \text{ or } G
      <400> 112
ctgactncta aacttctaat tcnatcaana taactactct ccttccgtct tncagagtgt
                                                                     60
tcacaataaa tctgtgaatc tggcatacac agttgctgga aaattgttct tcctccacna
                                                                     120
aaaggtcaat tgttcnccnc atgaaanaag ataaattgtt catccatcac tnctgaacca
                                                                     180
tccaaaacgc cggcggaatt attnccccgt tattatgggg aacggaattt tnaataaatt
                                                                     240
tgggaangaa tggggctttt attgttttgt tttccccctt tcttggcatt gattgggccg
                                                                     300
                                                                     360
caatgggccc cctcgctcan aanntgcccc ggggccggcc gctccaaaac cgaaattccc
                                                                     405
anccacactt ggcgggccgt tactanttgg atccgaactc ggtta
      <210> 113
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 113
                                                                      60
ggatagaaga gtatatgggt ttggcaccac ggggtggata ggcaaaacat ttggttgata
                                                                     120
aggcgcagat tctgaactaa cttgtaaggc ttgtctggtt ttaggacagg taaaatgggg
gaatggtaag gagagtttat aggttttagg agcccatgct gtagcaggca agtgataaca
                                                                     180
                                                                     240
ggctttaatc ctttcaaagc atgctgtggg atgagatatt ggcatttgag cggggtaagg
                                                                     300
360
tagaggtatc ttatacttgt ggggttaagg tgggggggat ataagaggga ggacgccaaa
                                                                     401
ggaggctttg gattaggaat aaggggcggc aatgagatgc a
      <210> 114
      <211> 401
      <212> DNA
```

```
<220>
      <221> misc feature
      <222> (1)...(401)
      <223> n = A, T, C \text{ or } G
      <400> 114
angtecacag gangeangag gecaggetee gteceancea gtecatgatg ttgaagagga
                                                                         60
ggaagcagca catggggttg aagaactgac tccacttccc aggactggtg gagctggtca
                                                                        120
ccatggctgt ggtggcgggg aagacggaca gggtgacttc tggaagacag tgaagactga
                                                                        180
aggitticct ggcttctggg gctcatctgg ctctgattcc ggctccttct ccaggicaag
                                                                        240
atccagggtt cagagctact ttcttggggg actactnggg aatcccgttc tcatctgggg
                                                                        300
gtngaggggg gacggggnaa gggncatgct tgtgacccag gtttcccacc tcqqcccqcq
                                                                        360
accacgctaa ggcccgaatt ncagcacact tggcggcccg t
                                                                        401
      <210> 115
      <211> 401
      <212> DNA
      <213> Homo sapien
      <400> 115
atccctgtaa gtctattaaa tgtaaataat acatacttta caacttctct tagtcggccc
                                                                        60
ttggcagatt aaatctttgc aaaattccat atgtgctatt gaaaaatgaa ataaaacctc
                                                                       120
agatgtctga attcttattt caaatacagt tatataatta ttttaaatta caatatacaa
                                                                       180
tttctgttaa atacaactgt taagggattc tgagaacaat tataagatta taataatata
                                                                       240
tacaaactaa cttctgaaat gacatgggtt gtttccttcc caccctccta ccctctcaaa
                                                                       300
gagtttttgc atttgctgtt cctggttgca aaaggcaaaa gaaaatctaa aaatagtctg
                                                                       360
tgtgtgtcca cgacatgctc gctcctttga gaatctcaaa c
                                                                       401
      <210> 116
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A,T,C or G
      <400> 116
ngatttaatt gnnagcttct ttttaatgga atnnttggct aaaatgaatt gatgattatg
                                                                        60
aatatcccta ggaggagtta gcatggannn tgatcatttt cttnqnactc ctttangaca
                                                                       120
nggaaacagg natcagcatg anggtancan aaaccttatn accnangege acganetgae
                                                                       180
ttcttccaaa gagttgnggt tccgggcagc ggtcattgcc gtgcccattg ctggagggct
                                                                       240
gattctagtg ntgcttatta tgctggccct gaggatgctt ccaanatgaa aataaqangc
                                                                       300
                                                                       301
     <210> 117
      <211> 383
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(383)
```

## <223> n = A,T,C or G

1220	, - , -				
<400> 117					
	tttat tgggcagtta	cnacaacnaa	tgttttcana	aaaatatttg	60
gaaaaaatat accac	ttcat agctaagtct	tacagagaan	aggatttgct	aataaaactt	120
aagttttgaa aatta	agatg cnggtanagc	ttctgaacta	atgcccacag	ctccaaggaa	180
nacatotcct attta	gttat tcaaatacca	gttgagggca	ttgtgattaa	gcaaacaata	240
tatttqttan aactt	tgntt ttaaattact	gntncttgac	attacttata	aaggagnctc	300
taactttcga tttct	aaaac tatgtaatac	aaaagtatan	ntttccccat	tttgataaaa	360
gggccnanga tactg					383
<210> 118					
<211> 301					
<212> DNA					
<213> Homo	sapien				
<400> 118			attaattatt	ttttt	60
ctgctagaat cacto	geeget gtgetttegt	ggaaatgaca	geteettget	ccctccccca	120
ctgtttttgt tttac	cattag tcattggacc	acagecatte	tectecacac	accttcattt	180
caaagaaatg aacag	gttgta gggagaccca	tatacattat	gtttgccatt	attacttata	240
tgaagttegg gtttt	ttgtgt taagttaatc atagtg tacggcaaaa	gedeatteat	ccactatctc	ragtgcttga	300
	alagig lacggeadaa	gagtattaat	CCCCCCCCCC	243234234	301
C					
<210> 119					
<211> 401					
<212> DNA					
<213> Homo					
	-				
<400> 119					
taaggacatg gacc	cccggc tgattgcatg	gaaaggaggg	gcagtgttgg	cttgtttgga	60
tacaacacag gaac	tgtgga tttatcagcg	, agagtggcag	cgctttggtg	tccgcatgtt	120
acgagagcgg gctg	cgtttg tgtggtgaat	ggggaggaaa	tgtcactgcc	gaagaccaaa	180
aacaagcttc ttgg	tataaa agactcttac	: agaatatgtg	tattgtaatt	tattgatctg	240 300
gatgettaag tgte	atggac agtaaatgaa	tttgaacttt	atgtttgagg	acatgacatt	360
gggtttgaaa atat	aaactg cttttgagca	gtttaagtca	gggcattiga	gaalaaaala	401
ggaactttct cttc	agtttg taaaactctc	tigecetete	C		401
010 100					
<210> 120					
<211> 301					
<212> DNA <213> Hom					
(213) HOW	o sapici				
<400> 120	ı				
	:agtcaa acctggagc	c aaaaaggaca	caaaggacto	tcgacccaaa	60
ctgccccaga ccct	ctccag aggttgggg	gaccaactca	tctggactca	gacatatgaa	120
gaagetetat ataa	atccaa gacaagcaa	c aaacccttga	tgattattca	tcacttgggt	180
gagtgccac acag	stcaagc tttaaagaa	a gtgtttgctg	, aaaataaaga	aatccagaaa	240
ttggcagage agtt	tgtcct cctcaatct	g gtttatgaaa	a caactgacaa	acacctttct	300
c					301
-210 > 121	ı				

<210> 121

<211> 2691

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      <210> 137
      <211> 269
      <212> DNA
      <213> Homo sapien
      <400> 137
                                                                        60
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atgagtttgt tagtttaaca tcatatattt gtaatagtga aacctgtact caaaatataa
                                                                       120
gcagcttgaa actggcttta ccaatcttga aatttgacca caagtgtctt atatatgcag
                                                                       180
atctaatgta aaatccagaa cttggactcc atcgttaaaa ttatttatgt gtaacattca
                                                                       240
                                                                       269
aatgtgtgca ttaaatatgc ttccacagt
      <210> 138
       <211> 452
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(452)
       <223> n = A, T, C \text{ or } G
       <400> 138
 ctccatggga ggcaaaatat agagaattta tggtgcccaa ctcttatgta atcactggac
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 taatcttccc tggtaactat gcaacatttg gacagaaagg cacacaaaaa agtttaaata
                                                                        120
 tttcatgtgc caatctggaa aaaaataatt taaatcaaca gaacagacag tacatctaca
                                                                        180
 caaatgagga aagcagaaaa gatacctcac attcatttat ctcaggtttc aaagtggctt
                                                                        240
```

```
caatgctaaa gtaaatgtat taacatttgg aaaatacaag acaatttttt tgtttgtttt
                                                                     300
360
aaaacaaaac aaaaaaggag ttcaggactt gttatcagtg tccaagtggc taanaactgg
                                                                     420
ttcccataac aagcattgaa agttaaggcc cc
                                                                     452
      <210> 139
      <211> 474
      <212> DNA
      <213> Homo sapien
      <400> 139
tgtgcctcat tgaggttaca attgaaacag atgtgagcac ctgagagact ttccctgatt
                                                                      60
atattected acaaaccact gtaccatatt accttatttt atettettga aattettatt
                                                                     120
cattggcttg tttgttgtct ctttgcatta gatatatgta agctccttgg cataaatttg
                                                                     180
acattggtag gggactgaca ttctaacctg gcccaggccc taggagagag ataactccac
                                                                     240
aaagcagcac atactatctt aggttagcag ggagctaact caccatgtag cagatgaaaa
                                                                     300
aaaccaaacc cagcactgtg cataaatacc acttgccaag aagtcaggtc ctcggcaacc
                                                                     360
gagaatcaac ctcagcacaa acgcagqtqq ctqqqctctq ttccccctta qccaccacct
                                                                     420
cagectetee ceteceetge eccaagtgee caagagettg getetetgtg ettt
                                                                     474
      <210> 140
      <211> 487
      <212> DNA
      <213> Homo sapien
      <400> 140
cttccctgcc tcgtgttcct gagaaacgga ttaatagccc tttatccccc tgcaccctcc
                                                                     60
tgcaggggat ggcactttga gccctctgga gccctcccct tgctgagcct tactctcttc
                                                                    120
agactttctg aatgtacagt gccgttggtt gggatttggg gactggaagg gaccaaggac
                                                                    180
actgacccca agctgtcctg cctagcgtcc agcgtcttct aggagggtgg ggtctgcctq
                                                                    240
tcctggtgtg gttggtttgg ccctgtttgc tgtgactacc ccccccctc cccgaaccga
                                                                    300
gggacggctg cettigtete tgccteagat gccacetgce ecgeceatge tecceateag
                                                                    360
cagcatccag actttcagga agggcagggc cagccagtcc agaaccgcat ccctcagcag
                                                                    420
ggactgataa gccatctctc ggagggcccc ctaataccca agtggagtct ggttcacacc
                                                                    480
ctggggg
                                                                    487
     <210> 141
     <211> 248
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(248)
     <223> n = A, T, C or G
     <400> 141
ttaaagatgg ggaaatgagg cctgnaaata gaaaagattt gcctagagtc acacacactg
                                                                     60
tCaggtcagg tagagtcaaa atcaggcacc ccgactcaca gactgcttca cattgccatc
                                                                    120
agagattgtc ctgcaacaat attatgttta gttctactgc agaatgataa ctggatctta
                                                                    180
ccccctttgc ctgatctggc cacaaacttg tttttcaggt ctttccatta ggctctcttc
                                                                    240
agctaatt
                                                                    248
```

<210> 142

<211> 173

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<212> DNA
      <213> Homo sapien
      <400> 142
tactaagatt gtccaagcct ccctcttaaa actttctttc cctttagagg aatcattact
                                                                       60
tegtattaaa agtttetaet teettgtaga atatetaeat eeaatgggee atggeacaaa
                                                                      120
atttaagtct agaaagaatc ttaaaggctc atcttatagt aaccagaggc agg
                                                                      173
      <210> 143
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(511)
      <223> n = A,T,C or G
      <400> 143
cetegteaga ggggtggtte etggtnacet gtactecacg gaceteggtg aagcaaaage
                                                                        60
ttcagggcag agggaatgag gcaacccagt ggcagccccg ctgggccccg tggctcctgc
                                                                       120
tetectattg gacgtagagg caggggagag acttetetat acaaatatte teateacaga
                                                                       180
agggatgate ettgetgete tgeegtaggg tttttgatge tgagetatge tgeacatgae
                                                                       240
gttaacctaa agaacttgga ctgagctttt aaaaaaggac agcaaacaat tttataatcc
                                                                       300
ttaaagtgta atagacggtt acactagtgc agggtattgg ggaggctctt tgggtgtgga
                                                                       360
ggctgtcact tgtatttatt gtgactctaa atctttgata gtaaaacaaa tgtaaaaaga
                                                                       420
aatgtttgcc accagatggg aatagaagtt ccaataagca ggctggaatg ggtggctata
                                                                       480
                                                                       511
 cgttgtatca cgaggaagtt ttagactctg a
       <210> 144
       <211> 190
       <212> DNA
       <213> Homo sapien
       <400> 144
 cattettetg teacatgeea atteagttgt caateceatt gtetatgett aceggaaceg
                                                                        60
 agacttccgc tacacttttc acaaaattat ctccaggtat cttctctgcc aagcagatgt
                                                                       120
 caagagtggg aatggtcagg ctggggtaca gcctgctctc ggtgtgggcc tatgatctag
                                                                       180
                                                                       190
 gctctcgcct
       <210> 145
       <211> 169
       <212> DNA
       <213> Homo sapien
       <400> 145
 gatgtggtta tctcctcaga tggccagttt gccctctcag gctcctggga tggaaccctg
                                                                        60
 cgcctctggg atctcacaac gggcaccacc acgaggcgat ttgtgggcca taccaaggat
                                                                        120
                                                                        169
 gtgctgagtg tggccttctc ctctgacaac cggcagattg tctctggat
       <210> 146
        <211> 511
        <212> DNA
        <213> Homo sapien
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<212> DNA

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<400> 146
                                                                        60
atctagagaa gatttgggaa acacatgata gctatggtta aatacttaac agggcaatca
cagggaagat gactagattt cctaacatcc atgagtgaaa tttatagaag tatactctct
                                                                       120
gacttgatat aaaggaagat tttaaaaaac atgactgttc aggagtgttc aagtagggtc
                                                                       180
agatgaccag tgattgggaa tacttcgtaa gcaggagcaa gtaagatctg agccactgtt
                                                                       240
ctatcggtag ggtgtctgtg qtattccttg qtcaaaqaaq tactctaagc aacttcaqtc
                                                                       300
tcacgaatta ctatcaccct cgtgggcata catgatggtt accctaaaga ggaagtttca
                                                                       360
                                                                       420
gaaggcagta atattggatc ctggaatagt cagacaggag ccttcatgca gatacccttt
tcagttctcc atacacccat tcacaagtgg tcacaaaaac acccagtacc tttacttggc
                                                                       480
tttacccact taacaatatg ctcaatatga g
                                                                       511
      <210> 147
      <211> 421
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc feature
      <222> (1)...(421)
     <223> n = A, T, C \text{ or } G
      <400> 147
gaccaqttqa gttcttcctq qctattqtat aatccacaqc cacactqtqa aaqcaaatct
                                                                        60
ggccagttag caacacaggg agaatctgcc tgaactgacc aaaggtgtcc atacttcatg
                                                                       120
tcagtgagaa tttcacctcc atcatqttct aaagagccaa caacagattc tagggcactq
                                                                       180
caaaatgctt cagcaattaa ttgaagttct gtttgagtac attcatcatc tttgagaatg
                                                                       240
ctttctgggt cgttgtgagt cttgtgtctg atatatgcag ccaaatgagt ttcagtacag
                                                                       300
ccacctccca acaaagccca tggttccttg agtgttaact gcaggacatg cagtgccgtc
                                                                       360
tgacacgtga gcttcagctc atcccangca gtgtcatttc tgttgcagag aagccaagct
                                                                       420
                                                                       421
g
     <210> 148
      <211> 237
      <212> DNA
      <213> Homo sapien
      <400> 148
acacaccact gttggccttc catctgggtt aagtcaactg tgagtagaaa ccgaagataa
                                                                        60
cagttttgta ttcataatgg ccttttcata ctccaagtac ttttgagcac agagcctctt
                                                                       120
gcttctgacc tggcacttgg aacacagata tatatatctt ttgttctgtc cctgggaaac
                                                                       180
tgatatttgt gtaagacaac caccagatat tttctctaat aaaatcttct aaaatta
                                                                       237
     <210> 149
     <211> 168
      <212> DNA
     <213> Homo sapien
     <400> 149
agagaaagtt aaagtgcaat aatgtttgaa gacaataagt ggtggtgtat cttgtttcta
                                                                        60
ataagataaa cttttttgtc tttgctttat cttattaggg agttgtatgt cagtgtataa
                                                                       120
aacatactgt gtggtataac aggcttaata aattctttaa aaggagag
                                                                       168
      <210> 150
     <211> 68
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<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(68)
      \langle 223 \rangle n = A,T,C or G
      <400> 150
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                                                                         60
                                                                         68
      <210> 151
      <211> 421
      <212> DNA
      <213> Homo sapien
      <400> 151
                                                                         60
aggtgacacg tattcgggat gaaagtataa tagtcattcc ttcaaccctt gcatttatgg
actctggaaa tcgaagatcc acagtgagta aagatgttcg tccaaagaca aaaaatagaa
                                                                        120
acageteaac aaagegagag acaaaaaaac aaaatggeac tgtggetetg eetttgaagt
                                                                        180
                                                                        240
ctgggctcca gcagagggct gatcttccca caggagacga gacggcctat gacactctcc
agaactgttg tcagtgccga attttacttc ccttgcccat tctaaatgag caccaggaga
                                                                        300
                                                                        360
agtgccagag gttagctcac caaaagaaac tccagtgggg ctggtgagat ggctcagcgg
gtaagagcac ccgactgctc ttccgaaggt ccggagttca aatcccagca accacatggt
                                                                        420
                                                                        421
g
      <210> 152
      <211> 507
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(507)
       <223> n = A, T, C \text{ or } G
       <400> 152
                                                                          60
 gaatteggea enagetegtg eegeeagggt nggteenttt tttgeteege etegeeanga
                                                                         120
 cttectacag ctategeeag tegteggeea egtenteett engaggeetg ggeggegget
 ccgtgcgttn tgggccgggg gtcgcctttc nctcncccag cattcacggg ggctccggcg
                                                                         180
 geogeggegt atecgtgtee teegeeeget ntgtgteete gteeteeten ggggeetaeg
                                                                         240
                                                                         300
 gctngctgct acngcggctt cctgaccgct tccnacgggc tgctggcngg caacgagaag
                                                                         360
 ctaaccatgc agaacctnaa cnaccgcctg gcctcctacc tgnacaaggt gcgcnccctg
 taggcggcca acggcnagct agaggtgaag atccnctact gggtaccaga agcaggggcc
                                                                         420
 tgggccctgc ccgactacag ccactnctnc acnaccatgc agtacctgcn ggganaagat
                                                                         480
                                                                         507
 tntngggngc caccatngag aactgca
       <210> 153
       <211> 513
       <212> DNA
       <213> Homo sapien
       <400> 153
                                                                          60
 gaattcggca cgaggtggct cagatgtcca ctactgggag tatggtcgaa ttgggaattt
 tattgtgaaa aagcccatgg tgctgggaca tgaagcttcg ggaacagtcg aaaaagtggg
                                                                         120
```

```
atcatcggta aagcacctaa aaccaggtga tcgtgttgcc atcgagcctg gtgctccccg
                                                                        180
agaaaatgat gaattetgea agatgggeeg atacaatetg teacetteea tettettetg
                                                                       240
tgccgcgccc cccgatgacg ggaacctctg ccggttctat aagcacaatg cagccttttg
                                                                       300
                                                                       360
ttacaagett cetgacaatg teacetttga ggaaggegee etgategage cactttetgt
ggggatccat gcctgcagga gaggcggagt taccctggga cacaaggtcc ttgtgtgtgg
                                                                       420
agctgggcca atcgggatgg tcactttgct cgtggccaaa gcaatgggag cagctcaagt
                                                                       480
agtggtgact gatctgtctg ctacccgatt gtc
                                                                       513
      <210> 154
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(507)
      <223> n = A,T,C or G
      <400> 154
ggcacgagct cgtgccgaat tcggcncgag cagacacaat ggtaagaatg gtgcctgtcc
                                                                        60
tgctgtctct gctgctgctt ctgggtcctg ctgtccccca ggagaaccaa gatggtcgtt
                                                                       120
actototgac ctatatotac actgggctgt ccaagcatgt tgaagacgtc cccgcgtttc
                                                                       180
aggccettgg ctcactcaat gacctccagt tetttagata caacagtaaa gacaggaagt
                                                                       240
ctcagcccat gggactctgg agacaggtgg aaggaatgga ggattggaag caggacagcc
                                                                       300
aacttcagaa ggccagggag gacatcttta tggagaccct gaaagacatc gtggagtatt
                                                                       360
acaacgacag taacgggtct cacgtattgc agggaaggtt tggttgtgag atcgagaata
                                                                       420
acagaagcag cggagcattc tggaaatatt actatgatgg aaaggactac attgaattca
                                                                       480
                                                                       507
acaaagaaat cccagcctgg gtcccct
      <210> 155
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(507)
      \langle 223 \rangle n = A,T,C or G
      <400> 155
ggcacgagga gacctaaggg ctgagtntcg ggaacaggag aaagctctgt tggccctcca
                                                                        60
gcagcagtgt gctgagcagg cacaggagca tgaggtggag accagggccc tgcaggacag
                                                                       120
ctggctgcag gcccaggcag tgctcaagga acgggaccag gagctggaag ctctgcgggc
                                                                       180
agaaagtcag tcctcccggc atcaggagga ggctgcccgg gcccgggctg aggctctgca
                                                                       240
ggaggccctt ggcaaggctc atgctgccct gcaggggaaa gagcagcatc tcctcgagca
                                                                       300
ggcagaattg agccgcagtc tggaggccag cactgcaacc ctgcaagcct ccctggatgc
                                                                       360
ctgccaggca cacagtcggc agctggagga ggctctgagg atacaagaag gtgagatcca
                                                                       420
ggaccaggat ctccgatacc aggaggatgt gcagcagctg cagcaggcac ttgcccagag
                                                                       480
ggatgaagag ctgagacatc agcagga
                                                                       507
     <210> 156
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<211> 509

<212> DNA

<213> Homo sapien

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<220>
      <221> misc_feature
      <222> (1)...(509)
      \langle 223 \rangle n = A,T,C or G
      <400> 156
                                                                        60
qqcacqaqqa caqaqaqaac cctgtngaaa gagcgttacc aggaggtcct ggacaaacag
aggcaagtgg agaatcagct ccaagtgcaa ttaaagcagc ttcagcaaag gagagaagag
                                                                        120
                                                                        180
qaaatgaaga atcaccagga gatattaaag gctattcagg atgtgacaat aaagcgggaa
gaaacaaaga agaagataga gaaagagaag aaggagtttt tgcagaagga gcaggatctg
                                                                        240
                                                                        300
aaagctgaaa ttgagaagct ttgtgagaag ggcagaagag aggtgtggga aatggaactg
                                                                        360
qatagactca agaatcagga tggcgaaata aataggaaca ttatggaaga gactgaacgg
gcctggaagg cagagatett atcactagag agccggaaag agttactggt actgaaacta
                                                                        420
                                                                        480
gaagaagcag aaaaagaggc agaattgcac cttacttacc tcaagtcaac tcccccaaca
                                                                        509
ctggagacag ttcgttccaa acaggagtg
      <210> 157
      <211> 507
      <212> DNA
      <213> Homo sapien
      <400> 157
                                                                         60
ggcacgaggg cagecetect accggegeae gtggtgeege egetgetgee teeegetege
                                                                        120
cctqaaccca qtqcctgcag ccatggctcc cggccagctc gccttattta gtgtctctga
                                                                        180
caaaaccqqc cttgtggaat ttgcaagaaa cctgaccgct cttggtttga atctggtcgc
                                                                        240
ttccggaggg actgcaaaag ctctcaggga tgctggtctg gcagtcagag atgtctctga
                                                                        300
gttgacggga tttcctgaaa tgttgggggg acgtgtgaaa actttgcatc ctgcagtcca
tgctggaatc ctagctcgta atattccaga agataatgct gacatggcca gacttgattt
                                                                        360
                                                                        420
caatcttata agagttgttg cetgeaatet etatecettt gtaaagacag tggettetee
                                                                        480
aggtgtaagt gttgaggagg ctgtggagca aattgacatt ggtggagtaa ccttactgag
                                                                        507
agctgcagcc aaaaaccacg ctcgagt
      <210> 158
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(507)
      <223> n = A, T, C \text{ or } G
      <400> 158
                                                                         60
ggcacgagtc gagctgtgcc tattcgngtc aatccaagag tgagtaatgt gaagtctgtc
                                                                        120
tacaaaaccc acattgatgt cattcattat cggaaaacgg atgcaaaacg tctgcatggc
cttgatgaag aagcagaaca gaaacttttt tcagagaaac gtgtggaatt gcttaaggaa
                                                                        180
                                                                        240
ctttccagga aaccagacat ttatgagagg cttgcttcag ccttggctcc aagcatttat
                                                                        300
qaacatgaag atataaagaa gggaattttg cttcagctct ttggcgggac aaggaaggat
                                                                        360
tttagtcaca ctggaagggg caaatttcgg gctgagatca acatcttgct gtgtggcgac
                                                                        420
cctggtacca gcaagtccca gctgctgcag tacgtgtaca acctcgtccc caggggccag
                                                                        480
tacacginity ggaagggcic cagigcanni ggccinacty chiacgiaat gaaagaccci
                                                                        507
gagacaaggn anctggnnct gnnacag
```

<210> 159 <211> 508 <212> DNA

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<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(508)
      <223> n = A,T,C or G
      <400> 159
ggcacnanaa accaggatta tggtnnggat ccaaagattg ctaatgcaat aatgaaqqca
                                                                        60
gcagatgagg tagctgaagg taaattaaat gatcattttc ctctcgtggt atggcagact
                                                                       120
ggatcaggaa ctcagacaaa tatgaatgta aatgaagtca ttagcaatag agcaattgaa
                                                                       180
atgttaggag gtgaacttgg cagcaagata cctgtgcatc ccaacgatca tgttaataaa
                                                                       240
agccagagct caaatgatac ttttcccaca gcaatgcaca ttgctgctgc aataqaaqtt
                                                                       300
catgaagtac tgttaccagg actacagaag ttacatgatg ctcttgatgc aaaatccaaa
                                                                       360
gagtttgcac agatcatcaa gattggacgt actcatactc aggatgctgt tccacttact
                                                                       420
cttgggcagg aatttagtgg ttatgttcaa caagtaaaat atgcaatgac aagaataaaa
                                                                       480
gctgccatgc caagaatcta tgagctcg
                                                                       508
      <210> 160
      <211> 508
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(508)
      <223> n = A.T.C or G
      <400> 160
ggcacgagct tggagcaaag tcatctnaag gaattagagg acacacttca ggttaggcac
                                                                        60
atacaagagt ttgagaaggt tatgacagac cacagagttt ctttggagga attaaaaaaag
                                                                       120
gaaaaccaac aaataattaa tcaaatacaa gaatctcatq ctqaaattat ccaqqaaaaa
                                                                       180
gaaaaacagt tacaggaatt aaaactcaag gtttctgatt tgtcagacac gagatgcaag
                                                                       240
ttagaggttg aacttgcgtt gaaggaagca gaaactgatg aaataaaaat tttqctqqaa
                                                                       300
gaaagcagag cccagcagaa ggagaccttg aaatctcttc ttgaacaaga gacagaaaat
                                                                       360
ttgagaacag aaattagtaa actcaaccaa aagattcagg ataataatga aaattatcag
                                                                       420
gtgggcttag cagagctaag aactttaatg acaattgaaa aagatcagtg tatttccgag
                                                                       480
ttaattagta gacatgaaga agaatcta
                                                                       508
      <210> 161
      <211> 507
      <212> DNA
      <213> Homo sapien
      <400> 161
ggcacgagcg ctaccggcgc ctcctctgcg gccactgagc cggagccggc ctgagcagcg
                                                                        60
ctctcggttg cagtacccac tggaaggact taggcgctcg cgtggacacc gcaagcccct
                                                                       120
cagtageete ggeccaagag geetgettte caetegetag ceeegeeggg ggteegtgte
                                                                       180
ctgtctcggt ggccggaccc gggcccgagc ccgagcagta gccggcgcca tgtcggtgqt
                                                                       240
gggcatagac ctgggcttcc agagctgcta cgtcgctgtg gcccgcgccg gcggcatcga
                                                                       300
gactateget aatgagtata gegacegetg caegeegget tgeatttett ttggteetaa
                                                                       360
gaatcgttca attggagcag cagctaaaag ccaggtaatt tctaatgcaa agaacacagt
                                                                       420
ccaaggattt aaaagattcc atggccgagc attctctgat ccatttgtgg aggcagaaaa
                                                                       480
atctaacctt gcatatgata ttgtgca
                                                                       507
```

<210> 165 <211> 462 <212> DNA

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<210> 162
      <211> 507
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(507)
      <223> n = A,T,C or G
      <400> 162
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gctctacggc tcacccaatg ctctggtgct actgattgct caagagaagg aaagaaacat
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atttgaccag cgtgccatag agaatgagct actggccagg aacatccatg tgatccgacg
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aacatttgaa gatatetetg aaaaggggte tetggaccaa gaccgaagge tgtttgtgga
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tggccaggaa attgctgtgg tttacttccg ggatggctac atgcctcgtc agtacagtct
                                                                       360
acagaattgg gaagcacgtc tactgctgga gaggtcacat gctgccaagt gcccagacat
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tgccacccag ctggctggga ctaagaaggt gcagcaggag ctaagcaggc cgggcatgct
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                                                                       120
ggttgagccc agtgacacca tcgagaatgt caaggcaaag atccaagata aggaaggcat
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ccctcctgac cagcagaggc tgatctttgc tggaaaacag ctggaagatg ggcgcaccct
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gtctgactac aacatccaga aagagtccac cctgcacctg gtgctccgtc tcagaggtgg
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gatgcaaatc ttcgtgaaga cactcactgg caagaccatc acccttgagg tggagcccag
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 tgacaccatc gagaacgtca aagcaaagat ccaggacaag gaaggcattc ctcctgacca
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                                                                        460
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       <211> 462
       <212> DNA
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 ggcctgtgcc atcagtatct taatgaagga cttggcagat gaacttgctc ttgttgatgt
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 aacaccaaag attgtctctg gcaaagacta taatgtaact gcaaactcca agctggtcat
                                                                        360
 tatcacggct ggggcacgtc agcaagaggg agaaagccgt cttaatttgg tccagcgtaa
                                                                        420
                                                                        462
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tcaqcttgaa gaactatgat ccccagaaqg acaagcgctt ctcgggcacc gtcaggctta
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agtccactcc ccgccctaag ttctctgtgt gtgtcctggg ggaccagcag cactgtgacg
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ataaaaaact qqtcaaqaag ctgqccaaqa aqtatgatgc gtttttggcc tcagagtctc
                                                                        360
                                                                        420
tqatcaaqca gattccacga atcctcggcc caggtttaaa taaggcagga aagttccctt
                                                                        462
ccctqctcac acacaacgaa aacatggtgg ccaaagtgga tg
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      <211> 459
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                                                                        120
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tggagettta atttattaat geanacagna eetaacaaac eeacangtee taaactaeca
agectqcatt aaaaattteg gntggggena eetennagea naacecaace teegageaac
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                                                                        300
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accaacagan caagntaccc tagggataac ancacaatcc tattctagac cccttatnac
                                                                       360
caatangntt tacacctona tngnggaacc aggacatccg atggggcagn cgttattaaa
                                                                       420
gttngttgnt aacnataaag tctacgtgat ctgagttag
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      <211> 464
      <212> DNA
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      <221> misc feature
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ttggtcacca gngctgcttt taactctggn aaagtggata ttgttgtcat naatgacccc
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theattqace thaactacat ggtttacatg ttecaatatg attecaecea tggcaaatte
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catngcaccg tnaaggctga gaacgggaag cttgtnatca atggaaatcc catcaccatc
                                                                       300
tttcangaac ganatcontn caaaaatcaa anttgggggc gatgcttggc cncttgaagt
                                                                       360
accepticaan gagaannnee ceaettigge egnintitine aaneeeaeee caattigggn
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<210> 168

aaaaaaaaa gggnntttgg gggggggct tttanntttt tttt

<211> 462

<212> DNA

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cancagttct cagacctgac agaggtgctt ttacacttcc taactgatcc anantangtg
                                                                        180
gaaatattnt tngttnatnt catntgaatn atccancncc aatcatanca nntttnattn
                                                                        240
                                                                        300
cctcataanc nttgagaana gcnnccttnt gnttncanan ggtgctntga anangagtct
cacangcaan caggtecaag eggatttnnt aactntgggt ettantgang agaaagneae
                                                                        360
                                                                        420
ttacttttct gaaancngga agcagaatgc tcccaccctt gctcgatggg ccatacgtca
                                                                        462
agactctgat gattaaccag ctttanatat ggacnggaaa tt
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      <211> 460
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      <221> misc_feature
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                                                                         60
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ccctccccac agatggtgca tcccctggca naggctcctg ctcacagcct cacttctaac
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cttctggaac ccgcccacca ctgccaagct cactattgaa tccacgccgt tcaatgnntc
                                                                         240
                                                                         300
ntaggggaag gaggngcttt ctactnttnc acaatctgan ccccttcttn tttggttact
ancatggctc tncatgtnaa aatactggna tggntaacct gtcaaattta taggnantnt
                                                                         360
                                                                         420
gctaattggg aaactnccnn tngtctaccc caggggnccc agattcctnn gttcncataa
                                                                         460
cnattaattt aacccctaat gncaanccct tngttaaaga
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       <211> 508
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       <221> misc feature
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                                                                         240
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                                                                         300
 tattaaagca gcggcagcgg ctgcacacag acatgatggc taggctaaaa caggaaggtc
 aagttgtttg gacagaaagg ctacagggtg cagtcctggc tcttgtgtaa gaattctgac
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 cacactaacc atgcctagga aggaaaggag ttgttctttt gtaagggatt gaggtttggg
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agattaatcg gacacgatca gcagggagag cacctgtgtt tttatgagaa ttatgctgag ataggtaaca gatgaggatg aaatttgg	480 508
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ctttgtggtt gggcaggatc cgggctcaga cgtcgccttc cacttcaatc cgcggtttga	240
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gcatgagcgg gcacgcatcg agaaggcgta tgcacagcag ctcactgagt gggcccgacg	240
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tgtcatgtct gaagcagaga gggtgagtga actgcacctg gaagtgaagg catcactgat	360
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tgaaaagacg aagcagcgac ttcagaatga agtggaggac ctcatgattg acgtggagag	360
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~211\square 407	

<211> 407

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<213> Homo sapien

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<210> 175 <211> 407 <212> DNA <213> Homb	sapien				
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<210> 176 <211> 409 <212> DNA <213> Homo	sapien				
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                                                                       360
ccacttaaca tctacaactt ccagccctgg ggttattgtc ccagaatcta g
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cgcacgatgc cctcggccac cagccacagc gggagcggca gcaagtcgtc cggaccgcca
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<210> 185 <211> 411 <212> DNA <213> Homo sapi	en				
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      <212> DNA
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gagaagatat taactctctt tgcatgactg tggttcagaa tcttatggag agaaataacc
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gaatcgacac aactaatgca tgctat
                                                                       506
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      <211> 506
      <212> DNA
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gtggaaatga cattgccttc cacttcaacc ctcgytttga agatggaggg tacgtggtgt
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360

420

480 503

WO 00/37643 62

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105

110

PCT/US99/30909 WO 00/37643 63

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70

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                                                                    240
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gggggaaact tgagaagaga agaaagaagc aagaaaaaaa gactttcaat tgtataaaat
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                                                                       300 -
caacagcaaa caaaaccaga atgaataagc ctttggcaga caattttaga aatttgaatg.
                                                                       360
ttacatttct caataattca caaacaatat attatatggt atatttatat taaatattgg
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gaaaccaatg ttgtaaattt gatgettata atgetttage caatgagage acaatgatat
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caatcaagct aaatgaatgc tggtgttatc acaacagtgc tcatttatga aacaa
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caggcagcgt ttggaaacct tttattatat agttgtttac atacttataa gtctatcatt
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attacctatg ggtttatatc ctcaaatacg acattctagt caaagtcttg gtaatataac
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tatagattac tatggaacca gacttacaag aacgcaatta tatccataaa tattttt	actgagtatt	actaatgaaa	catttagaaa	480 508
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acactcatgg atatgtaaaa actgtcaaga ttaaaattta atagtttcat ttatttgtta
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ttttatttgt aagaaatagt gatgaacaaa gatccttttt catactgata cctggttgta
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catctatctg agtagtcaaa atacaagtaa aggagagcaa ataaacaaca tttggaaaaa
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                                                                        374
aaaaaaaaaa aaaa
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gtctttgtgt tatgatcaat gaagaagggc cggccgtttg gcgctatcct catttcccag
                                                                        120
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                                                                        120
 atattaaaaa ggaaactaat tggaccattt tctatttgtc tattttatac aaaaaggcta
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 cacaattgat acactctatt cagataacaa tcaattagag tgantatgaa ttactggcga
                                                                        240
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 actaccgaga gact
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atccaagtta tacatgaata gaaaaagatg gtgttaaatt tgtgtgtagg ctgggaattc
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      <221> misc_feature
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                                                                       120
acactetgae acatgetetg agaatactgg gaetgetgtt teaaaaaaaa aggtteaaae
                                                                       180
ttattgtcac agcatcatca caaaatagag gatcaccatt ggtttgcttg gcttttcttt
                                                                       240
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                                                                       300
ttcacatcaa gagtacccca agaaaaacga aatccatggc acanacactg tacaagggtg
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cagggcaggg ctctgagggg cccaaacccc attttgccaa ctcgattttc tagcattgaa
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tggctacaca ctctcactac acacacagac cccacagtcc tatatgccac aaacacattt ccataacttg aaaatgagta ttttgcatat ctcagttcag gatatgttt ttacaagtta	240
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tgtggcgagt cagctaaata ctttgacgcc ggtggggata gcgatgatta tggtagcgga	360 420
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gataaaccct aggaagccaa ttgatatcat agctcagacc atacctatgt atccaaatgg	540
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aagaatataa acttcagggt gaccgaaaaa tcagaatagg tgttggtata gaatggggtc tcctnctccg cggggtcnaa gaaggtggtg ttgangttgc cggnctgtta ntagtatagn	660
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ggcacaggag gatctctaaa gcagtagcca aacaccactt tgtaaaagga ctcttccatc
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      <211> 374
      <212> DNA
      <213> Homo sapien
      <400> 250
aaaaaacaaa acaatgtaag taaaggatat ttctgaatct taaaattcat cccatgtgtg
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atcataaact cataaaaata attttaagat gccggaaaag gatactttga ttaaataaaa
                                                                       120
acactcatgg atatgtaaaa actgtcaaga ttaaaattta atagtttcat ttatttgtta
                                                                       180
ttttatttgt aagaaatagt gatgaacaaa gatccttttt catactgata cctggttgta
                                                                       240
tattatttga tgcaacagtt ttctgaaatg atatttcaaa ttgcatcaag aaattaaaat
                                                                       300
catctatctg agtagtcaaa atacaagtaa aggagagcaa ataaacaaca tttggaaaaa
                                                                       360
aaaaaaaaa aaaa
                                                                       374
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      <211> 356
      <212> DNA
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      <400> 251
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tgttctgggt gataattttg aattgatacc tgttcctttt tctgggtttt gttggctttt
                                                                       120
tgaaaaattg tctttcctta tcattggtgg gaggcttggt agcaaagtaa cattttttgg
                                                                       180
aaaagaggac agaaaaattg aactacagct tgagaacgta ttctttttt cctactttqt
                                                                       240
tattgcaaat tgaggaatca cttttaactg ttttaggtgt gtgtgtccag agtgagcaag
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gattatgttt ttggattgtc a	aaagaggatg	cttagtctta	aaataaaaat	aaattt	356
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<210> 253 <211> 379 <212> DNA <213> Homo sapie	n				
<pre>&lt;400&gt; 253 aaaaagcgct tagacttccc tctccaattc cttcagcaag attcatgtat aacttggatc aaagattgga taaatcagaa agcagcactg taggcagccc aaatgatcca accaccaaaa tataactcca aggacttgg</pre>	aattcccagc acacaccagt gaggcttttt aaaacaccc	ctacacacaa atataacgac ggtcttgaat aaacagtttt	atttaacacc aaaagataaa tcttcaccca ataagtgtag	atcttttct tgtataataa ctaacaatga acaccacttc	60 120 180 240 300 360 379
<210> 254 <211> 387 <212> DNA <213> Homo sapie	en				
<220> <221> misc_featu <222> (1)(387) <223> n = A,T,C	7)				
<pre>&lt;400&gt; 254 aaatttgact tttcagtgcc aggccnttga taattggcac agaagggtaa ctcggctaca gccatgaagc tcagagcatt ataacagact tacataggtg tatgagaatg aaagggtgtg ttctcatgta aatcagagaa</pre>	tatggaaatc gtaacagctt agctgaccct ggcctaaagc aaattgacta	ctgcaagatc aattttgtta tgaactattc aagctcctta	ccactacata aatttgttct aaatgggcac actgagcaaa	tgtgtggagc ttatactgga attagctagt atttggggct	60 120 180 240 300 360 387
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      <223> n = A, T, C \text{ or } G
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agcacctttg ataaaatata cttttgtgaa caaaaattga gacatttaca ttttctccct
                                                                        120
atgtggtcgc tccagacttg ggaaactatt catgaatatt tatattgtat ggtaatatag
                                                                        180
ttattgcaca agttcaataa aaatctgctc tttgtatgac agaat
                                                                        225
      <210> 256
      <211> 544
      <212> DNA
     <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(544)
      <223> n = A,T,C or G
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ccttgcttaa agcccagaag tggtttaggc ntttggaaaa tctggttcac atcataaaqa
                                                                        60
acttgatttg aaatgttttc tatagaaaca agtgctaagt gtaccgtatt atacttgatg
                                                                       120
ttggtcattt ctcagtccta tttctcagtt ctattatttt aqaacctagt cagttcttta
                                                                       180
agattataac tggtcctaca ttaaaaataat gcttctcgat gtcagatttt acctgtttgc
                                                                       240
tgctgagaac atctctgcct aatttaccaa agccagacct tcagttcaac atgcttcctt
                                                                       300
agcttttcat agttgtctga catttccatg aaaacaaagg aaccaacttt gttttaacca
                                                                       360
aactttgttt ggttacagtt ttcaggggag cgtttcttcc atgacacaca gcaacatccc
                                                                       420
aaagaaataa acaagtgtga caaanaaaaa aacaaaccta aatgctacty ttccaaagag
                                                                       480
caacttgatg gttttttta atactgagtg caaaaggnca cccaaattcc tatgatgaaa
                                                                       540
tttt
                                                                       544
      <210> 257
      <211> 420
      <212> DNA
      <213> Homo sapien
      <400> 257
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                                                                        60
agcaatttga taaaatatac ttttgtgaac aaaaattgag acatttacat tttctcccta
                                                                       120
tgtggtcgct ccagacttgg gaaactattc atgaatattt atattgtatg gtaatatagt
                                                                       180
tattgcacaa gttcaataaa aatctgctct ttgtatgaca qaatacattt qaaaacattg
                                                                       240
gttatattac caagactttg actagaatgt cgtatttgag gatataaacc catagqtaat
                                                                       300
aaacccacag gtactacaaa caaagtetga agteageett ggtttggett cetaqtqtca
                                                                       360
attaaacttc taaaagttta atctgagatt ccttataaaa acttccagca aagcaacttt
                                                                       420
     <210> 258
      <211> 736
      <212> DNA
     <213> Homo sapien
     <400> 258
aaacaaaatg ctaaacctaa aaacattqtt ctqtcaqttc ccaaattaaa tctacttaga
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ctaaaatcct ccatgttttc aagtatggaa atagaactca aatattccac aatacagtac	180
taaacagatg gagtatttag gaaagacttt gttgtcatat ggcacaatat taatattttg	240
ttgcttcaat acgttttgaa ataaatatca gatttttgtt ttttttcct aaaagaccaa	300
aattataatc tacattaaga taattctgac tgtggttaag acttaagagt gtaaaataca	360
acatcaatat tttatcacaa aagtaaagct ggtaacaaat tataaaagga gccagtactc	420
tactgagaca ggctcggaga ttaaagctca tcatgataga aatagtcatc atggagctgt	480
ctgccataat ctgtggcttc actggtgaga aacaagtccg ggttttccag aatctcttct	540
tcagagagct ttttgtcacc attcaaatcc atttcatcaa ttagatgaag cgcctcctct	600
tgtgcaatgc cctgattatt aggtctaccc aaggtaacag ctcttgggga tcaagcctgc	660
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ggatetteat ttgcag	736
994666646 469469	
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<213> Homo sapien	
(215) Homo Sup 25.1	
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<223> n = A,T,C  or  G	
(225) H = A,1,6 OF G	
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tatttttctt ttgctttatt aggtcacaca aaacagaatg aattagcaga aaaatgtatg	180
ttataaaaca gcatttacta cttcaattta attttttta ctaacaattg tggacctttt	240
tgatgacact tatgtatgtt tttaataaat tatgtactta ttagtactta atgagccctt	300
cotgoctcaa tataaaatta ctaaacttgg agaattacag attttattgt aggccctgat	360
gttagtcact ttggagaagc taaaaatttg gaaatgatgt aattcccact gtaatagcat	420
agggattttg gaagcag	437
agggatttig gaagtag	
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<212> DNA	
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(213) 110mo Bapton	
<400> 260	
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gaacaaaatg tcatgacaaa agtcattgag tacaagactt gtaataaaaa ggcataaaat	180
atatttatac ataaacccct ttcaaaaaac aagggaaagc ttgagccctc aatatagggc	240
gacacacgga gcgggtgacc gtgcaggtac aggtactgta ctgatttaaa gtcaagcact	300
gadadadyya gogyytyado grycagytad agyraddyd degaddrafa greddyddol	360
agagatagtg gattaatact cttttgccgt acactatata cagatgtata gtacaagtaa	420
caatggcaaa cagaatgtac agattaactt aacacaaaaa cccgaacatc aaaatgaagg	480
tgtgtggagg aaaggtgctg ctgggtctcc ctacaactgt tcatttcttt gtggggcagg	540
gggtagttcc tgaatggctg tggtccaatg actaatgtaa aacaaaaaca gaaacaaaaa	592
aaacaaggaa ctgtcatttc cacgaaagca cagcggcagt gattctagca gg	عرد
.210. 261	
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<211> 450	

<212> DNA

<213> Homo sapien

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agaaaattga gaagtaaacc agaaagttac agaatgtctg aaggggacag tgtgggagaa
                                                                        120
tccgtccatg ggaaaccttc ggtggtgtac agatttttca caagacttgg acagatttat
                                                                        180
cagtcctggc tagacaagtc cacaccctac acggctgtgc gatgggtcgt gacactgggc
                                                                        240
ctgagctttg tctacatgat tcgagtttac ctgctgcagg gttggtacat tgtgacctat
                                                                        300
gccttgggga tctaccatct aaatcttttc atagcttttc tttctcccaa agtggatcct
                                                                        360
tccttaatgg aagactcaga tgacggtcct tcgctaccca ccaaacagaa cgaggaattc
                                                                        420
cgcccttca ttcgaaggct cccaqagttt
                                                                        450
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      <211> 239
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      <213> Homo sapien
      <220>
      <221> misc feature
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      \langle 223 \rangle n = A,T,C or G
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                                                                         60
ttacttgcat aaataatatt ttcacttagt acaggctatt aatataagta atgagaattt
                                                                        120
aagtattaac tcaaaaaaag atagaggctc caaacttttc taagaaatta atgcattttc
                                                                        180
aaagtaataa tataatcaat ctgtaagtca aaagtaattt catattcatt gccaaattt
                                                                        239
      <210> 263
      <211> 376
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(376)
      <223> n = A, T, C \text{ or } G
      <400> 263
aaaaaaaaaa aaaaaaaatt ccttgtngtt tnttagagga aaaaaaqaaa aaccccaact
                                                                        60
tttancactg atactacata ttgctctgtt aaagaatttt ctctqccaaa aaaaaqaaaa
                                                                        120
aacaaaaaaa cgcttaaagc tggagtttga cattctgctt tcagatgctq tctttttatt
                                                                        180
agtgagtgat gatggtttgc taataatcaa taggtaataa ttttttgtaa tcccatcaaq
                                                                       240
tggctccata tgtttctgct ctctcgtgac tgtgttaatg tttaactgtt qtaccttaaa
                                                                       300
gccgaaatca gtaactatgc atactgtaac caaggtattg ggcttacaga gttqtttqtt
                                                                        360
gnataaagaa aatttt
                                                                        376
      <210> 264
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 264
aaattagcat tccacaaata tacaggtaat ttaataatta ttgtgcatga atacatacac
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aatgcttata tatacaaatt ccagtttgtt ttcatgtgct ggcaagggat ttgtatacaa
                                                                       120
tcataagctg tgttcatatt ggtcccattg aatattcaca atacaaaagc acaaaagaac
                                                                       180
cattgattta caaaaggaaa tctattt
                                                                       207
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<210> 265
      <211> 388
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A,T,C or G
      <400> 265
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aaagncenet gaaactgett ceactgeetg ttgtatagaa atgggtaaat tataaaggtg
                                                                       120
attcaatttg gagctccttc cttttttata gcacttctaa gctgtgtgcg cgacacacac
                                                                       180
cacagaggta ggaaggacca cctttaataa attatcttct taatcgcaga gaatttctga
                                                                       240
agataaaact gacaaaatgc taaaccaagg ctttgatgag tcccaaagga ccacagatcc
                                                                       300
atcggctcct atttgaagaa ttcatcccct gtagtgttct agcctttgta gggcactgga
                                                                       360
                                                                       388
ttacaagatc caccagggct ctgaacaa
      <210> 266
      <211> 616
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(616)
      <223> n = A,T,C or G
      <400> 266
                                                                        60
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aagacaagct gaatacatat ctatgttctg aataagtcca ctatggatat atataggaag
                                                                       120
agatatacat atatccatcc acagatacac acacacatat atattctgc atgtatatat
                                                                       180
                                                                       240
acataattct ttctatagtt acaggaaata cttcttctat aattctgatt ttgactccca
                                                                       300
tectecacea titacteate caeteattae etaaatettg getitette etatatigta
                                                                       360
aataatccat ccaaacttct agccagtact gtcaggaggg ttcttgctcg agtgagctgt
taatactatt ttccactgac aacttctgca catcgaggac acagtgtatc tgaagactcc
                                                                       420
gctgtatact tccaacaacg ggggcatttt tctttcgtag tcggcatgac aattacttta
                                                                       480
taggaagact cttcacgaat atcaccacct tctaagttga tgaggaattt ccctttaagc
                                                                       540
tegattacat etgeagteat etetegtggt teetgaceag taaagttgae teagaageea
                                                                       600
                                                                       616
tcattaattc attcaa
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       <211> 341
       <212> DNA
       <213> Homo sapien
       <400> 267
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                                                                         60
                                                                        120
 ttattcttgt tgtattgtca tttgagtttt gtatatattt ttgatattaa ccccttgtca
 catgtataat ttgcaaatat tttctccctt tttttagttg tcacattctg ttcattgtat
                                                                        180
                                                                        240
 cagattctgt gcagcagctt tttaatttga agtgatctga ctgacttgtt cttccttttg
 tgtcctggga tatttaggtt aaatcaaaaa acttgctgcc cagaccaatg ttatggggct
                                                                        300
                                                                        341
 ttcactctat tttttggtag tagtagttta agagttttag g
```

```
<210> 268
      <211> 367
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(367)
      <223> n = A, T, C \text{ or } G
      <400> 268
                                                                          60
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gacgintcct tctagagagc aaatctatca taaaatgtca aaactagaag agaataaaat
                                                                         120
gaaaggaaaa aacctagaaa aatatcctaa aatatcaaat gcagtcattt ctaaatataa
                                                                         180
qccataatta taqctttacc tattqttctt attqttccta tgctgcttct acaatgttac
                                                                         240
atcaactata cttagcttta ctctcccaaa atcttggtga tgaagccttc tgagtgtgct
                                                                         300
                                                                         360
ttccaatgtg ccagaaccag aagggcattc caaggcttcc ccacatttcc tccatttacg
gagacag
                                                                         367
      <210> 269
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(270)
      \langle 223 \rangle n = A,T,C or G
      <400> 269
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                                                                          60
gnaangengn tgaggtggat taaaccaaac ccagctacgc aaaatcttag catactcctc
                                                                         120
                                                                         180
aattacccac ataqqatqaa taataqcaqt tctaccqtac aaccctaaca taaccattct
                                                                         240
taatttaact atttatatta tootaactac tacogcatco ctactactca acttaaacto
                                                                         270
cagcaccacg accctactac tatntcgcac
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      <211> 368
      <212> DNA
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      <220>
      <221> misc feature
      <222> (1)...(368)
      <223> n = A, T, C \text{ or } G
      <400> 270
ctgaatcatg aataacacta tataatagag tntaaggaac acaagcatta gatgtgatcc
                                                                          60
ttgccccata cccttagatt atgtcagact aaagctgaca attctgccag gctctgaacc
                                                                         120
cctaqtqccc ccaacccaaa tcttggaagc aaagaatatg ccctgtcata caactttgta
                                                                         180
caagttgtag taaaacaaag cttaagtttt ctcatctttc tacagcaaat ggtcagttat
                                                                         240
ttaataaaca ctaaaatgct cctaagaatc cattttgagt ttgtttacca aacacattgt
                                                                         300
qcaaqaactq actacacaaa aagtteettt gaaatttggt ccacaaatte acttaaggtt
                                                                         360
                                                                         368
ggaaattt
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<210> 271
      <211> 313
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(313)
      \langle 223 \rangle n = A,T,C or G
      <400> 271
                                                                          60 .
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agacaanngt ttgcaaacac atgtccaatt caggaaaaaa aatttcacgt ttctcgtctg
                                                                         120
gettttttet tetttttat ttgtttggga gatteceage tagttteaga ettggtetgt
                                                                         180
gaaggaggca cactattttg cttggtattt gacttggatt tatctgtctc ttgtagtatt
                                                                         240
ggcggcactt gggaagagct cttgtcagaa tcactttttg ataagattac agatggctcg
                                                                         300
                                                                         313
qtaqaagtag cag
      <210> 272
      <211> 462
      <212> DNA
      <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (462)
       \langle 223 \rangle n = A,T,C or G
       <400> 272
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                                                                          60
tacaaaatct atatacttgc acatttagta tttgtcaatg tgccagaggt tttcttcatg
                                                                          120
 aaatttgact totttgaagt gaaggotttt ttotatoato tottatagot otgactgaat
                                                                          180
 aagtettaat getttettea tgttttetat caataggggt aaateeegag geteatatgt
                                                                          240
 gtacaatctg ttagagtatc ttccagctat gtcagctcta actgttaaag aagggtctac
                                                                          300
 aaacatgatt ctaggcacat attgcccatc aggtgataaa ttcttatcag tggtttcatg
                                                                          360
 cataaggttt agcatgatga acttattctg agccatttct tgtatttctt cattttgggc
                                                                          420
                                                                          462
 aaatactttc tttagtgctt gagagtattg acaatcctcc ag
       <210> 273
       <211> 282
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
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       <223> n = A,T,C \text{ or } G
       <400> 273
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                                                                           60
 tacatnncat ttcatattat ataattctgc ttattctttc aaaaatttat acatccattg
                                                                          120
 ggcaaggaat ggttttcatt aaattaccaa tattaaatgc acttaatcat tgtgtatagg
                                                                          180
 ttaaaccaaa gtaactatta actaactttt aggcatttta aggaggtaaa acatacattt
                                                                          240
                                                                          282
 tacacataag tatttgatgc aaatatgcag ataaaatttt tt
```

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<210> 274
      <211> 125
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(125)
      <223> n = A, T, C \text{ or } G
      <400> 274
cagocotaga cotoaactao otaaccaach tinottaaaa taaaatooco actaigcaca
                                                                         60
ttnaatenet ccaacatact cggattetac cetageatca cacacegeac aateceetat
                                                                        120
                                                                        125
ctagg
      <210> 275
      <211> 528
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(528)
      \langle 223 \rangle n = A,T,C or G
      <400> 275
                                                                         60
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ataaqccnqq aaccacaaat aattaaaagg aaacacagca atcccataaa caagcattct
ggcatctgtt agaaattttc cctcaaatta tgaaatgtag ctctccatgc tttccaatga
                                                                        180
ttgttataat acccacaaat atctgtgatt tcagtggaat actttaacaa aagttttctt
                                                                        240
tttaaggcat gatcctgatt cattttttct tcaatatctc agtcatttca ggaactacct
                                                                        300
taaataaatc tgcaactatt ccataatctg ccacttggaa aattggagct tctgggtctt
                                                                        360
                                                                        420
tattaattqc cacaattqtc ttqctgtctt tcatcccagc taaatgttgg atggctccag
atattccaac agcaatataa agttctggtg ctactatttt tcccgtctgn ccaacttgca
                                                                        480
tgtcattggg aacaaagcca gcatcaacag cagcacggga agcaccaa
                                                                        528
      <210> 276
      <211> 420
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(420)
      \langle 223 \rangle n = A,T,C or G
      <400> 276
aaatgtcttg tttcccagat ttcaggaaan tttttttctt ttaagctatc cacagcttac
                                                                         60
agaaacctga taaaatatac ttttgtgaac aaaaattgag acatttacat tttctcccta
                                                                        120
tgtggtcgct ccagacttgg gaaactattc atgaatattt atattgtatg gtaatatagt
                                                                        180
tattgcacaa gttcaataaa aatctgctct ttgtatgaca gaatacattt gaaaacattg
                                                                        240
gttatattac caagactttg actagaatgt cgtatttgag gatataaaacc cataggtaat
                                                                        300
aaacccacag gtactacaaa caaagtctga agtcagcctt ggtttggctt cctagtgtca
                                                                        360
attaaacttc taaaagttta atctgagatt ccttataaaa acttccagca aagcaacttt
                                                                        420
```

```
<210> 277
      <211> 668
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (668)
      \langle 223 \rangle n = A,T,C or G
      <400> 277
ccagggtggc tctgatatag cagccctggt ntattttcga tatttcagga agactggcag
                                                                         60
atngcaccag accetgaatt ettetagete etceaatece attttatece atggaaceae
                                                                        120.
taaaaacaag gtctgctctg ctcctgaagc cctatatgct ggagatggac aactcaatga
                                                                        180
aaatttaaag ggaaaaccct caggcctgag gtgtgtgcca ctcagagact tcacctaact
                                                                        240
agagacagge aaactgcaaa ccatggtgag aaattgacga cttcacacta tggacagctt
                                                                        300
ttcccaagat gtcaaaacaa gactcctcat catgataagg ctcttacccc cttttaattt
                                                                        360
gtccttgctt atgcctgcct ctttcgcttg gcaggatgat gctgtcatta gtatttcaca
                                                                        420
agaagtaget teagagggta acttaacaga gtateagate tatettgtea ateecaaegt
                                                                        480
tttacataaa ataagagatc ctttagtgca cccagtgact gacattagca gcatctttaa
                                                                        540
cacagoogtg tgttcaaatg tacagnggtc cttttcagag ttggacttct agactcacct
                                                                        600
gttctcactc cctgttttaa ttcaacccag ccatgcaatg ccaaataata gaaattgctc
                                                                        660
                                                                         668
cctaccag
      <210> 278
      <211> 202
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(202)
      <223> n = A, T, C \text{ or } G
       <400> 278
                                                                          60
aaattggtat cgacggcaac caggggaagn tnctaaactc ctaatctatt ctggatccaa
                                                                         120
ttngcnaagt ggggtcccat caaggttcag tggcagtgga tctgggacag atttcactct
cacgatcage agtetgeaac eegaagattt tgeaacttae taetgteaac agagttaeat
                                                                         180
                                                                         202
gtccccgtac acttttggac cc
       <210> 279
       <211> 694
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(694)
       <223> n = A, T, C \text{ or } G
       <400> 279
 ctgtacttgg acaaaataag ttaattctat ttggttgtcc attaaagttt tatgtggcta
                                                                          60
 tgnacccact ggagctaaaa attggctttt aactgtttcc aaatcagaac tagcagagga
                                                                         120
 gagaagtaaa taaagccaat ggcactccct tcagaggctc aaaatggtta gattttgatg
                                                                         180
```

```
cagatttaac cttagcgagt ttcagtcagt ccatttagat gatcctgtag gttcatacaa
                                                                        240
 atacactgaa ccgttggttt aacttctctt ccttcctcaa agtttatgat aaagagactc
                                                                        300
 atccctgtat tgggagtgac tgacataagt tcagatctgc tcagagtggc tggtaaggaa
                                                                        360
 cacttaaggt cagtcagaaa ataatcaaac agacttctca tgtaagcacc gtgactcaca
                                                                        420
 actaagacac tggctgctaa tcctggaata ccgctgtctg aattaacttt agagctgtga
                                                                        480
 ttttttccta aaggaaatat ctctgccaaa gaagtttcca gacagntgct tqqqaqatcc
                                                                        540
 ttggggaaaa ctggtctttt tgatccggtt ctttcangan taggtngaca aaagaaatnc
                                                                        600
 aaaaaaagnet ateeeacgen tttnteacet gggeeeageg gnneteetee nggggggggn
                                                                        660
 aaacacangg gactcttccc ngggctngct tnng
                                                                        694
       <210> 280
       <211> 441
       <212> DNA
       <213> Homo sapien
       <400> 280
 aaaaaaacttc catgcaactt ctggtttatt gtttggcaac tccacatgat aaaaaaataa
                                                                         €0
 anacagecca acegagette ggaattaage acteteetag taagegatte aaaceteqtaa
                                                                        120
 tatttgccac aggactgact tatttattta ctagctagaa gctcttaagt tcacttgttt
                                                                        180
 atcagggcat atacagaagg gtttgttaaa actcgatgtt aactttacaa ctttctgacc
                                                                        240
 tggtgcatga attotcaagt actgtatttc actgtgttgg tgtgtctgat ggaaatttcq
                                                                        300
aygtggtccc acaaaaatat tttatgtagt gtgccttcaa agagaaccat ttatttctct
                                                                        360
teacttateg teccaeaaag teacatttgg tggtggteag eeaagtegea tetggtetag
                                                                        420
 ttttactctt gtcccaattt t
                                                                        441
      <210> 281
      <211> 398
      <212> DNA
      <213> Homo sapien
      <400> 281
aaatttgtta ggtctgaaga atctaaaact gttaatttaa cccttaactt gtgcctagaa
                                                                        60
actacagcac atataaaata tgtaaacacc agcctgttgc tgtacttttc tgcttatttt
                                                                       120
acagcctcaa atatttctca ttatcttgtc acttagttct tcatgtttct ccttctgact
                                                                       180
tttaataatg gtaataggaa aacaaaaccc aaagcttttc agaacttcag tgtgaggttt
                                                                       240
cctattttga caagttaact tgtaaatact caggttttac gatgtataat ttacctaata
                                                                       300
gaccaaacta actcatggag atattttgaa ctattattta ggtacaaact ttataaagaa
                                                                       360
tgttagtatg tcataaaata taacattaca qcttattt
                                                                       398
      <210> 282
      <211> 226
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(226)
      <223> n = A,T,C or G
      <400> 282
aaaacaatat tototttttg aaaatagtat naacaggoca tgcatataat gtacagtgta
                                                                        60
ttacnccaat atgtaaagat tcttcaaggt aacaagggtt tgggttttga aataaacatc
                                                                       120
tggatettat agacegttea tacaatggtt ttageaagtt catagtaaga caaacaagte
                                                                       180
ctatctttt ttttggctgg ggtgggggcg cccaggccga ggctgg
```

```
<210> 283
      <211> 358
      <212> DNA
      <213> Homo sapien
      <400> 283
aaacaaaaat actcaagatc atttatattt ttttggagag aaaactgtcc taatttagaa
                                                                        60
tttccctcaa atctgaggga cttttaagaa atgctaacag atttttctgg aggaaattta
                                                                       120
gacaaaacaa tgtcatttag tagaatattt cagtatttaa gtggaatttc agtatactgt
                                                                       180
actatecttt ataagteatt aaaataatgt tteateaaat ggttaaatgg aceaetggtt
                                                                       240
tettagagaa atgtttttag gettaattea tteaattgte aagtacaett agtettaata
                                                                        300
cactcaggtt tgaacagatt attctgaata ttaaaattta atccattctt aatatttt
                                                                        358
      <210> 284
      <211> 288
      <212> DNA
      <213> Homo sapien
      <400> 284
aaaacttttg ttaagaaaaa ctgccagttt gtgcttttga aatgtctgtt ttgacatcat
                                                                         60
agtctagtaa aattttgaca gtgcatatgt actgttacta aaagctttat atgaaattat
                                                                        120
taatgtgaag tttttcattt ataattcaag gaaggatttc ctgaaaacat ttcaagggat
                                                                        180
ttatgtctac atatttgtgt gtgtgtgtgt gtatatatat gtaatatgca tacacagatg
                                                                        240
                                                                        288
catatgtgta tatataatga aatttatgtt gctggtattt tgcatttt
       <210> 285
       <211> 629
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(629)
       <223> n = A, T, C \text{ or } G
       <400> 285
 cctaaaagca gccaccaatt aacaaagcgt ncannctcaa cacccactac ctaaaaaaatc
                                                                         60
 ccaaacatat aactgaactc ctcacaccca attggaccaa tctatcaccc tatanaagaa
                                                                         120
 ctaatgttag tataagtaac atgaaaacat tctcctctgc ataagcctgc gtcagattaa
                                                                         180
 aacactgaac tgacaattaa cagcccaata tctacaatca accaacaagt cattattacc
                                                                         240
 ctcactgtca acccaacaca ggcatgctca taaggaaagg ttaaaaaaag taaaaggaac
                                                                         300
 teggeaaate ttacecegee tgtttaceaa aaacateace tetageatea eeagtattag
                                                                         360
 aggcaccgcc tgcccagtga cacatgttta acggccgcgg taccctaacc gtgcaaaggt
                                                                         420
 agcataatca cttgntcctt aattagggac ctgtatgaat ggcttcacga gggttcagct
                                                                         480
 gtctcttact tttaaccagt gaaattgacc tgcccgtgaa gaggcnggca tgacacagca
                                                                         540
 agacgagaag accctatgga gctttaattt attaatgcaa acagnaccta acaaacccca
                                                                         600
                                                                         629
 caggtcctaa acttacccaa accctggca
        <210> 286
        <211> 485
        <212> DNA
        <213> Homo sapien
```

<400> 286

```
120
ttaaaaccta taqcaatcat ttcaaatcta ttctqcaaat tgtataagaa taaagttaga
attaacaatt ttattttgta caacagtgga attttctgtc atggataatg tgcttgagtc
                                                                       180
cctataatct atagacatgt gatagcaaaa gaaacaaaca aaagccagga aaacactcat
                                                                       240
                                                                       300
tttcqccttg aatatgtaaa tgggattaat tttgtcctgt gccttatgtg gaaaggaact
                                                                       360
tctttggttt tcctttttg ttctggtgga agcatgtgca ggagacatat catccaaaca
taaaccatta aaatgtttgt ggtttgcttg gctgtaattt tcaaagtagt taattgagga
                                                                       420
caaaqqqtaa tgcagaagtg atagctttgg tttgctgagt cttgttttaa gtggccttga
                                                                       480
                                                                       485
tattt
      <210> 287
      <211> 340
      <212> DNA
      <213> Homo sapien
      <400> 287
                                                                        60
cctggagtcc aataaccacc ccctcatacc acaccctgtg catacaccag ccaagccttt
cctggtctgg gaagggaaga gaaaaaagac gcaggccacc tgggggttct gcagtctttg
                                                                       120
gtcagtccag ccttctatct tagctgcctt tggcttccgc agtgtaaacc ttgcctgccc
                                                                       180
ggaggcagga ggcccagctg gacctccgag ggccatgagc aggcagcagc catcttggcc
                                                                       240
teaagettge ettteeettg agteeetete teecetegge tetageeaga ggtgtageet
                                                                       300
                                                                       340
gcagatctag gaagagaaga gctggggagg aggatgaagg
      <210> 288
      <211> 290
      <212> DNA
      <213> Homo sapien
      <400> 288
aaacagtoto tootoggtgt totoottgto aaactgttoa toocagttto ototgaaata
                                                                       60
gacagcattc accagaacca gccttgtcaa tggatccact gagcccggag agagcaactc
                                                                       120
                                                                       180
cgcaatttta ccttctgtct tttcagctac ccaggtgttt atgtgttttc tggacttctc
                                                                       240
tacggcgctg ataaagtcaa gctcctccat ctctgcttgg tagaattttt ggcaggaatc
                                                                       290
tctaaaagat gagaggaaat cacaagactt ttccccaaag agcctgttgg
      <210> 289
      <211> 404
      <212> DNA
      <213> Homo sapien
      <400> 289
ccacccacgc traggition atcacactga tgactccggg triggcgagc acaggagcgc
                                                                        60
aaaccttttc acattctttc tgtgatccaa atttgttttc gtttccacca caacctccat
                                                                       120
                                                                       180
accagaatct tgcacagctt ttggtgtttg gatcatagta ccattttaat atgaaatccc
tgcaagttcc ttcgtctttc ggcaacttgc atatatctgt ttcagtgaga gccaatggtt
                                                                       240
ctgtgctcac cattagattg atggttgaac tagaagctga ccttgctggc tgtggaggtg
                                                                       300
ggggctgaga tttctttgta ctgaaacttc cgtggtaggt ggctctgacc tgagacctca
                                                                       360
                                                                       404
ggtagcagac cacagccaca tggtatgtct gcccagcgag cagg
      <210> 290
      <211> 384
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

```
<222> (1) . . . (384)
      <223> n = A,T,C \text{ or } G
      <400> 290
ccaggcgctc cttgtcggca tcagggaggg tggccttgaa ctgctcatgg gctgtggtca
                                                                        60
gtccctggat ctcctcaatg gtgtgcacaa tgaaggtgtc ctgcaggtcc tccatggccc
                                                                       120
cctccatcca gttgttgaag ggtgcagccc gcttggcata ctccaagtac agctggtcaa
                                                                       180
tggtctccag cagtttctcg gtccgctcca gagcttccct tcgcttctga gttagggccc
                                                                       240
ccagattgtc ccactggtca cagatctttt ggcaacgggc gttgacactg ggtgagtcat
                                                                        300
aatantecag eteattgage teetgtgega tggeggeaat etgeteeaca eggteetggt
                                                                        360
                                                                        384
gggcagccag gccactctcg aagg
      <210> 291
      <211> 278
      <212> DNA
      <213> Homo sapien
      <400> 291
aaagtttatt tttactattt.ctttatcact ttattgtatc atcaccattg gtttcataat
                                                                         60
gtaaatacta tatgttgaac aaattaaatg tcaaaatttt.ttattaccat agtccatgtt
                                                                        120
aatagtgggg ctttcaggtg tttagagatt ttttttgttg ttgttaacat tcattgcaaa
                                                                        180
agtactagat ggtgtataac tctagagttg aattttaagg gattccctaa tatgtatact
                                                                        240
                                                                        278
atctttttat ctgaagtaat aaataaacaa tgatcttg
       <210> 292
       <211> 177
       <212> DNA
       <213> Homo sapien
       <400> 292
cettggcccg gtcattcttg tccagtttga taggttcagg aaattcgttg tacagctcca
                                                                         60
 ceteegttte etgettaagt geatteegtg caategtetg gaacgeetge tecaegttga
                                                                        120
 tggcctcctt ggcactggtc tcaaagtagg gaatgttgtt tttgctgtag caccagg
                                                                        177
       <210> 293
       <211> 403
       <212> DNA
       <213> Homo sapien
       <400> 293
 aaaaagaagg acttagggtg tcgttttcac atatgacaat gttgcattta tgatgcagtt
                                                                         60
 tcaagtacca aaacgttgaa ttgatgatgc agttttcata tatcgagatg ttcgctcgtg
                                                                         120
 cagtactgtt ggttaaatga caatttatgt ggattttgca tgtaatacac agtgagacac
                                                                         180
 agtaatttta totaaattao agtgoagttt agttaatota ttaataotga otoagtgtot
                                                                        240
 gcctttaaat ataaatgata tgttgaaaac ttaaggaagc aaatgctaca tatatgcaat
                                                                         300
 ataaaatagt aatgtgatgc tgatgctgtt aaccaaaggg cagaataaat aagcaaaatg
                                                                         360
 ccaaaagggg tcttaattga aatgaaaatt taattttgtt ttt
                                                                         403
       <210> 294
       <211> 305
       <212> DNA
       <213> Homo sapien
       <220>
        <221> misc_feature
```

```
<222> (1)...(305)
      <223> n = A, T, C \text{ or } G
      <400> 294
60
tatgggtgga agttggagag aaggacattt tggctttgta catgaaaaga ctctccagat
                                                                   120
agaaacagat tctgcccata agtgaaataa aatgctttgt gggggtaatg agtgacttat
                                                                   180
agtattcagg cagatgttac ataactgcta attaagtttc cctggattga ntttanncaa
                                                                   240
anaattgaaa gtngattttg gtcangtgtc agnaaactac tgcctataaa cccatatcnt
                                                                   300
accca
                                                                   305
      <210> 295
      <211> 397
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(397)
     \langle 223 \rangle n = A,T,C or G
     <400> 295
cctatctggt tggccttttt gaagacacca acctgtgtgc tatccatgcc aaacgtgtaa
                                                                   60
caattatgcc aaaagacatc cagctagcac gccgcatacg tggagaacgt gcttaagaat
                                                                  120
180
cctgttattg gtagttctga acgttagata tttttttcc atggggtcaa aaggtaccta
                                                                  240
agtatatgat tgccgagtgg aaaaataggg gacagaaatc aggtattggc agtttttcca
                                                                  300
tttncatttg tgggngaatt tttaatataa atgcggagac gtaaagcatt aatgcnagtt
                                                                  360
aaaatgtttc agtgaacaag tttcagcggt tcaactt
                                                                  397
     <210> 296
     <211> 447
     <212> DNA
     <213> Homo sapien
     <400> 296
ccatcctcga tgttgaagtt gtcgtggggc ccgaagacgt tggtggggat gacagcggtg
                                                                   60
aaggtgcagc cgtactgctg gaagtaggcc ctgttctgca cgtcgatcat cctcttggca
                                                                  120
tacgagtacc caaaattgct gttgtgggga ggcccattgt ggatcatggt ctcatctatc
                                                                  180
gggtaggtcg tcttgtcagg gaagatacag gtggacaggc aggacaccac cttgcgggcg
                                                                  240
cccacctcga aggccgagtg caggacgttg tcgttcatgt gcacgttttt cctccagaag
                                                                  300
tccaaattgt atttgatatt ccggaacagg cccccacca ttgcagcaag atggatgacg
                                                                  360
tgtgtgagtt ggaccttctc aaacagggcg cgggtctgtg ctgtatccgt gagatcggcg
                                                                  420
tctttagagg agacaaacac ccagtcc
                                                                  447
     <210> 297
     <211> 681
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(681)
     <223> n = A, T, C or G
```

```
<400> 297
aaataacagc atgtaaaata ttaaaataca agctttcaaa aataaataca taaataagta
                                                                      60
gaaccetegt aagaaatagt caaacacatt aagteettte cagetgteee tagaaagetg
                                                                     120
ctgttctctt tttcattttc agctctggta agggcaggga ccaccctgca ggaagtgtca
                                                                     180
atgatacgct gataagcttc ttacttctct cctgtcagtt ggtgctcccc ctgtgatgag
                                                                     240
aaaagggtta ctgttgcagg tgctaaggaa ggctgctctt ctgtcactct gaagttgctt
                                                                     300
ggagggatgt ccccatgcag actctctccc agccctccac tcagggaagg tctgtctgta
                                                                     360
cccactgcct totatagcag aaaacttgca ctcctgaatg ctttttttt ttttcaagaa
                                                                     420
agaagnggct gnggactcaa ctagattctt ggtttgaaaa agccaaaaca tattggtcac
                                                                     480
tgattgtcac attgggttag aaatgtccat tcatgatctc ccttaagctg cacacaaccc
                                                                     540
                                                                     600
tatgaaataa ctaccattat ctaccctatt ttgctaaagc tcaaagagat taaataatgt
tgacagggat cttagccttg aactcactga aggngttact gcaaagttct gctcttcacc
                                                                     660
                                                                     681
aaqaaqqntt'acaggccaaa g
      <210> 298
      <211> 353
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (353)
      \langle 223 \rangle n = A,T,C or G
      <400> 298
60
                                                                      120
geoceaenet gneeecteee tgeocecaeg tetecageaa cacaaggegg eeagtggaee
gtgaaccatt tatttccaaa ctataaagaa acctgctctc tgagaaaana cactgcccag
                                                                      180
qngatgaagc tccagcccct ggaggtccaa aacccagtcc aaactcagtc cctttagaaa
                                                                      240
gctgctgtgc cttggaaatg annntcggnt gtcanagcct gggaagtggt gggaagaacc
                                                                      300
 ageccaetee ceteteetge tgegatteea gegenegttg ggneeagate tgg
                                                                      353
       <210> 299
       <211> 560
       <212> DNA
       <213> Homo sapien
       <400> 299
 aaagttcaag gactaacctt atttatttgg gaaagggag gaggaaggaa atgatatggt
                                                                       60
 acccagacac tgggctaggc tgcaacttta tctcatttaa tactcccagc tgtcatgtga
                                                                      120
                                                                      180
 gaaagaaagc aggctaggca tgtgaaatca ctttcatgga ttattaatgg atttaagagg
 gcatcaatca gctcaactca agatttcata atcattttta gtatttagat tgtgcctcaa
                                                                      240
                                                                      300
 agttgtagta cctcacaata cctccactgg tttcctgttg taaaaacctt cagtgagttt
 gaccattgtg ctcttggctc ttgggctgga gtaccgtggt gagggagtaa acactagaag
                                                                      360
 tctttagtac aaaactgctc tagggacacc tggtgattcc tacacaagtg atgtttatat
                                                                      420
 ttctcataaa gagtcttccc tatcccaagg tcttcatgat gccagtagcc atatatgata
                                                                      480
 aattatgttc agtgataact tagttatcag aaatcagctc agtggtcttc cccgccatga
                                                                      540
                                                                      560
 ttcacatttg atgagttttt
       <210> 300
       <211> 165
       <212> DNA
       <213> Homo sapien
```

<220>

```
<221> misc feature
      <222> (1)...(165)
      <223> n = A, T, C \text{ or } G
      <400> 300
aaaaactaca taggggtgtg tgtgtgtgtg tatgtttatt ttatacacac atatttgtat
                                                                         60
attctaatat attactaagg caattttaat gaattaccat gtatataaaa aaatatctgn
                                                                        120
cacttggcac acaggtttgt atgtatgtgt atatatat gtatg
                                                                        165 ·
      <210> 301
      <211> 438
      <212> DNA
      <213> Homo sapien
      <400> 301
aaaatatatg tatttaaaaa caaaaagcaa cagtaatcta tgtgtttctg taacaaattg
                                                                         60
ggatctgtct tggcattaaa ccacatcatg gaccaaatgt gccatactaa tgatgagcat
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atctttggaa tgagtaggca agacgatttt tacctattat ttctatgttg tgggtaatgt	347
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gradeatite agacagetee atqttqccct tagtgctgte tgacegaage etgtetgtee	180
tragatataa agatgaagcq caqctqtata aagaagagca cctgaggaat cggcagcacc	240
ctcactgcta cgttcagtac atgatcgcca tcatcaacaa ctgccagacc ttcaaggaat	300
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<212> DNA

<213> Homo sapien

<400> 358

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<210> 359 <211> 411 <212> DNA <213> Homo sapien	
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aageggeege etteteeteg tactgetggg tgaggntete gateteette tggaacetet tetteeete tteeagaget teeaeggnge tggeaaagte etgeagette ttettegagt eggagagetg gatgttga	300 360 378
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                                                                       120
tggggtcccc aggatgaaaa cgacaatgtg cctttttatt attatttatt tggtggtcct
                                                                       180
gtgttattta agagatcaaa tgtataacca cctagctctt ttcacctgac ttagtaataa
                                                                       240
                                                                       300
ctcatactaa ctggtttgga tgcctgggtt gtgacttcta ctgaccgcta gataaacgtg
tgcctgtccc ccaggtggtg qgaataattt acaatctgtc caaccagaaa agaatgtgtg
                                                                       360
tgtttgagca gcattgacac atatctactt tgataagaga cttcctgatt ctctaggtcg
                                                                       420
gttcgtggtt atcccattgt ggaaattcat cttgaatccc attgtcctat agtcctagca
                                                                       480
ataagagaaa tttcctcaag tttccatgtg cggttctcct agctgcagca atactttgac
                                                                       540
                                                                       544
attt
      <210> 363
      <211> 328
      <212> DNA
      <213> Homo sapieri
      <400> 363
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                                                                       120
gecattatat tigattitge attactgitt cacaatgaag cittetitaa ggettigatt
                                                                       180
tttatgatta tgaaagaaat aaggcacaac cacagttttt ctttcttaaa tttcatcact
                                                                       240
gttgatgtgg ttcttttgtg ttaaaaaaaa aaagtgcaac tatcaaaact aaaaaattat
                                                                       300.
                                                                        328
agagtaatat tgccgttctg ctgatttt
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       <211> 569
       <212> DNA
       <213> Homo sapien
       <400> 364
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                                                                        120
 ggaacagact cccttttcta aaactgaact tgaccacatc aaaagtttgt aaaacaatct
                                                                        180
 ccatggtaat taaacttgca ttcaacacca tatggtaaca gaagatggca aaggataaga
                                                                        240
 ttcagatctt agatctttcc aagtagggca tgttagatga tagaaggatt agttgcaagc
                                                                        300
 tggatctgag ctcaggcttg ggcatgaagg aaactgtctc ccatgtggtt tggaagagtt
                                                                        360
 aggggctccc tgagctctat tgtgaactat acgggtttca tccaaggaat ggtatgatgt
                                                                        420
                                                                        480
 gggcataaaa ccattcttca gacaactgaa gatggtcccc ttctgtagcc agaaacacta
 gctgtcctgc attgtccatt tcctttagcc ccaggeggtc ctgtgtgtac agggaggtct
                                                                        540
                                                                        569
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       <211> 151
       <212> DNA
       <213> Homo sapien
       <400> 365
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aaaaaaaaa atccttttat tatggaattt gtcaaacaca cacacaagca taacaaaccc

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ctaggtaccc atctccaagt tttgacccct attataattt catcttcagt gttttattat
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ccacttcctc tctctctatc tttagtattt t
                                                                       151
      <210> 366
      <211> 508
      <212> DNA
      <213> Homo sapien
      <220>
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                                                                       120
catcaacage enceantnta enceacacta gaargtacae teeggeaagt aaattaaggn
                                                                      180
tgcagtccat ccctgaacga tganaagngg tctgagctat ggcaaagngt tanaaaqtag
                                                                      240
cccagctana caaatgcccc agctatcccc aggggagtta ttcagtactt aanacttcat
                                                                      300
ttccaananc agccccggaa aagccctgac aggaaggggg gaccagngat caccgatntc
                                                                      360
ccattagggg cggncaccaa aaacaaaatg cctggagctt ntgagcagct gcagcctggg
                                                                      420
gttgtggcta ggcncngggn gnggttgcaa aaaaacggct gtntccgggg agaggcaaat
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ggcaggccag ccagccctgg gtacatgg
                                                                      508
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      <211> 382
      <212> DNA
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      <400> 367
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attgaccact gggatgcagt caacctggaa tgctttgaag aggacccagg gcgcaagtgg
                                                                      180
atggacaget tgeteagtaa ettggggtge eagtetgeet eteatgtagg gecetteate
                                                                      240
gatagctacc gctgcttcca accaaagcag gagggggcct tcacctgctg gtcagcagtc
                                                                      300
actggcgccc gccatctcaa ctatggctcc cggcttqact atqtqctqqq qqacaqqacc
                                                                      360
ctggtcatag acacctttca gg
                                                                      382
      <210> 368
      <211> 174
      <212> DNA
      <213> Homo sapien
      <400> 368
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tgatgagatc cctgggacag aaccccactg aagcagagct gcaggatatg atcaatgagg
                                                                      120
tggatgcaga tgggaacggg accattgact tcccggagtt cctgaccatg atgg
                                                                      174
      <210> 369
      <211> 216
      <212> DNA
      <213> Homo sapien
      <400> 369
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ttgcccttgg acttttccaa ggtatattat ggggttttat gcaaaattcc aagctaccat
                                                                       120
gtaacttttt ttaaccattt aacaaggagg gggaactgtt tcctaccttc tttacatgtt
                                                                       180
                                                                       216
gtgcattgtt gtggtccaga aatgccaaac cttttt
      <210> 370
      <211> 344
      <21.2> DNA
      <213> Homo sapien
      <400> 370
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                                                                        60
                                                                       120
aaataactac acatggaaat gaaactagct gaagcetttt cttgttttag caactgaaaa
ttgtacttgg tcacttttgt gcttgaggag gcccattttc tgcctggcag ggggcaggtc
                                                                       180
                                                                       240
tgtgccctcc cgctgactcc tgctgtgtcc tgaggtgcat ttcctgttgt acacacaagg
gccaggetee atteteete cettteeace agtgccaeag cetegtetgg aaaaaggace
                                                                       300
                                                                        344
aggggtcccg gaggaaccca tttgtgctct gcttggacag cagg
      <210> 371
      <211> 741
      <212> DNA
      <213> Homo sapien
      <220>
       <221> misc feature
       <222> (1) . . . (741)
       <223> n = A, T, C \text{ or } G
       <400> 371
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 gctaagtgta gcagtttgtt ccctgctaca ctccaaggca caaaggagtt caaggaatgt
                                                                        120
                                                                        180
 gcaatggaaa tcagttagat gaatgtgtta ggaaccttcc ctttaataaa gctggatccc
 acactagece ctacacecte teateaceaa atatteetge tteeteteae etgeaettge
                                                                        240
                                                                        300
 tgttctctcc tctgccacac aaatctacct ctcaagccta ggtcccacct gcttcatgac
 aactttccag actattccag aacctttaac catctctgac ctctcatcag atctatgttg
                                                                        360
 tacataacac caattaatga gatcattact gctttatgct ctaattgctt cctgtattca
                                                                        420
 aaatcttctc tccaaccaca taatgactcc ctaaacttct cttgtatttt ccaatgcctt
                                                                        480
 gtacaagcac agaactggtc aatcaataaa tactcactgg tratttgagg aaaaaatgtt
                                                                        540
 gccaagcacc atctttatca gaaaataaat caattcttct aaacttggag aaatcaccct
                                                                        600
                                                                        660
 attcctagta tgtgatctta attagaacaa ttcagattga gaangngaca gcatgctggc
                                                                        720
 agtecteaga gecetegett geteteggna ectecetgee tgggeteeca etttggtgge
                                                                        741
 atttgaggag cccttcagcc t
       <210> 372
       <211> 218
       <212> DNA
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       <220>
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       <223> n = A,T,C or G
        <400> 372
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agtgagaaat ctaccacctt ctacagtage cccagatcae eggacacaae aeteteaeet gecageaega caageteagg egteagtgaa gaateeaeea eeteeeaeg eegaceagge teaaegeaea caacageatt eeetggeagt aeettggn	120 180 218
<210> 373 <211> 168 <212> DNA <213> Homo sapien	
<400> 373	60
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<210> 374	
<211> 154 <212> DNA	
<213> Homo sapien	
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$\langle 223 \rangle$ n = A,T,C or G	
<400> 374	<b>.</b>
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caacgcacac aacagcattc cctggcagta cctc	154
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<211> 275 <212> DNA	
<213> Homo sapien	
<400> 375	
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gctgctgtgg gaagttgtag aatgccgact gaggcctggc gtggtggtgc tgtcagggaa	180 240
tgctgttgtg tgcgttgagc ctggtcggct gtgggaggtg gtggattctt cactgacgcc tgagcttgtc gtgctggcag gtgagagtgt tgtgg	275
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<220>	
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<222> (1)(191) <223> n = A,T,C or G	
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ctgactggag cctgaggtgg tggtgctggc aggtaacagt gttgtatccg ttgagcctgg gctgctgtgg gaagttgtag aatgccgact gaggcctgcc gtggtggtgc tgntagggaa	120 180

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191
tgctgctagc g
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      <211> 476
      <212> DNA
      <213> Homo sapien
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tgttaatttc ctgcagctcc tggttggttc tggagcagat gatctcaatg agagagtcct
                                                                     120
cgtcggttcc cagccccttc atggaagctt ttagctcaga agcgtcatac tgagcaggtg
                                                                     180
tetteaatag geceaaaate acegteteea ggtggeeaga taaggetgae tteagtgetg
                                                                     240
                                                                     300
atgcaagttc ctttttggtc cttctctggt aggcgaaggc aatatcctgt ctctgtgcat
tgctgcggtt ggtcaaaatg ttgacaatgg tgacctcatc cacacctttg gtcttgatgg
                                                                     360
ctgtttcaat gttcaaagca tcccgctcag catcaaagtt agtataggct ttgacagacc
                                                                     420
catatgcact tgggggtgta gagtgatcac cctccaagcc gagcttgcac aggatt
                                                                      476
      <210> 378
      <211> 455
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(455)
      \langle 223 \rangle n = A,T,C or G
      <400> 378
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                                                                       60
aatcatattg tcagttgtcc aaagcagctt gaatttaaag tttgtgctat aaaattgtgc
                                                                      120
aaatatgtta aggattgaga cccaccaatg cactactgta atatttcgct tcctaaattt
                                                                      180
cttccaccta cagataatag acaacaagtc tgagaaacta aggctaacca aacttagata
                                                                      240
300
agaaacaaat ttcaaaataa atcacatctt ctcttaaaac ttggcaaacc cttccctaac
                                                                      360
tgtccaagtn tgagcataca ctgccactgg ctttagatac tccaattaaa tgcactactc
                                                                      420
                                                                      455
tttcactggt ctgaatgaag tatggtgaaa caagc
       <210> 379
       <211> 297
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(297)
       \langle 223 \rangle n = A,T,C or G
       <400> 379
                                                                       60
 ageteggate cetagnacgg cegecagtgt getggaatte gecettageg geggeeeggg
 caggtacaaa gaatccttag acgccatact gagttttaag ttccttaatt cctaatttaa
                                                                      120
 ggcttctagt gaagcctcct cacagtaggc ttcactaggc ccacagtgcc cctagacctc
                                                                      180
                                                                      240
 tgacaatccc accctagaca gactttattg caaaatgcgc ctgaagaggc agatgattcc
 caagagaact caccaaatca agacaaatgt cctagatctc tagtgtggna gaactat
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```

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<211> 144
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(144)
      <223> n = A, T, C or G
      <400> 380
                                                                        60
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ctattttttt qnqttttttt qtttttaaat caataaqtaa tctaggacta gcattatgtt
                                                                        120
tgctagacct ggcatttgct cggc
                                                                        144
      <210> 381
      <211> 424
      <212> DNA
      <213> Homo sapien
      <400> 381
actictigaat acaagtitict gataccactg cactgictga gaatticcaa aactitaatg
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aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa taattaattt
                                                                        120
catgggacta aatgaactaa tgaggataat attttcataa ttttttattt gaaattttgc
                                                                       180
tgattettta aatgtettgt tteecagatt teaggaaaet ttttttettt taagetatee
                                                                       240
acayettaca qeaatttqat aaaatataet tttgtgaaca aaaattgaga catttacatt
                                                                       300
ttctccctat qtqqtcgctc cagacttggg aaactattca tgaatattta tattgtatgg
                                                                       360
taatatagtt attgcacaag ttcaataaaa atctgctctt tgtataacag aatacatttg
                                                                       420
aaaa
                                                                       424
      <210> 382
      <211> 408
      <212> DNA
      <213> Homo sapien
      <400> 382
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                                                                        60
                                                                       120
aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa taattaattt
catgggacta aatgaactaa tgaggataat attttcataa ttttttattt gaaattttgc
                                                                       180
tgattcttta aatgtcttgt ttcccagatt tcaggaaact ttttttcttt taagctatcc
                                                                       240
acagettaca geaatttgat aaaatataet tttgtgaaca aaaattgaga catttacatt
                                                                       300
                                                                       360
ttctccctat gtggtcgctc cagacttggg aaactattca tgaatattta tattgtatgg
                                                                       408
taatatagtt attgcacaag ttcaataaaa atctgctctt tgtatgac
      <210> 383
      <211> 455
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(455)
      <223> n = A, T, C or G
      <400> 383
actettgaat acaagtttet gataceactg cactgtetga gaattteeaa aactttaatg
                                                                        60
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<210> 384 <211> 376 <212> DNA <213> Homo sapien	ı				
<220> <221> misc_featur <222> (1)(376) <223> n = A,T,C c					
<pre>&lt;400&gt; 384 actcttgaat acaaggttct g aactaactga cagcttcatg a catgggacta aatgaactaa t tgattcttta aatgtcttgt t cacagcttac agcaatttga t tttctcccta tgtgggcgct o ggaatatagc attgcc</pre>	aaactgtcca gaggataat ttcccagatt taaaatatac	ccaagatcaa attttcataa tcaggaaact ttttgngaac	gcagagaaaa tittttattt tttttttctt aaaaattgag	taattaattt gaaattttgc ttaagctatc acatttacat	60 120 180 240 300 360 376
<210> 385 <211> 422 <212> DNA <213> Homo sapier	n			·	
<pre>&lt;400&gt; 385 acctgtgggt ttattaccta t tggtaatata accaatgttt t acttgtgcaa taactatatt t ggagcgacca catagggaga t tatcaaattg ctgtaagctg t aacaagacat ttaaagaatc a ttagttcat ttagtcccat tc</pre>	tcaaatgtat accatacaat aaatgtaaat tggatagctt agcaaaattt	tctgtcatac ataaatattc gtctcaattt aaaagaaaaa caaataaaaa	aaagagcaga atgaatagtt ttgttcacaa aagtttcctg attatgaaaa	tttttattga tcccaagtct aagtatattt aaatctggga tattatcctc	60 120 180 240 300 360 420 422
<210> 386 <211> 313 <212> DNA <213> Homo sapie	n				
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<210> 387
      <211> 236
      <212> DNA
      <213> Homo sapien
      <400> 387
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                                                                      60
cacaacaaaa ctaactaata ctaacatctc agacgctcag gaaatagaaa ccqtctqaac
                                                                     120
tatectgeec gecateatee tagteeteat egeceteeca teectaegea teetttacat
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                                                                    120
agagettaaa tetttaaatt attteeatag tettaaaaaa tatgtaatgt cagaatgeat
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ataaaaagaa tgtaaaagga aacctaaaat acaaatggaa taatgtaaca aataaatatt
                                                                    240
tgatttcagt aactgttaat aatcagctca acaccaccat tctctctaaa ctcaatttaa
                                                                    300
ttcttatagg aataatgaac tgtcaaatgc catggcataa ttatttattt ccaaqctatc
                                                                    360
atcaatgatt agaactaaaa aaaatttggc ataaaaaaat cacaattcag cataaataaa
                                                                    420
gctattttta gcttcaacac tagctagcat ctctaagaat tgttgaaata agt
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<210> 391 <211> 216

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gtctgaaaat gtaatatttt gataatactg taatatacct gtcacacaaa tgcttttcta
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atgctgaatt gtgatttttt tatgccaaat ttttttaa
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                                                                        120
ttgacatgtg ccagggcaat gatgaatgag aatctacccc cagatccaag catcctgagc
                                                                        180
aactcttgat tatccatatt gagtcaaatg gtaggcattt cctatcacct gtttccattc
                                                                        240
                                                                        300
aacaagagca ctacattcat ttagctaaac ggattccaaa gagtagaatt gcattgaccg
                                                                        360
cgactaattt caaaatgctt tttattatta ttatttttta gacagtctca ctttgtcgcc
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caggccggag tgcagtggtg cgatctcaga tcagtgt
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                                                                         120
 aatgagaatc tacccccaga tccaagcatc ctgagcaact cttgattatc catattgagt
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 caaatggtag gcatttccta tcacctgttt ccattcaaca agagcactac attcatttag
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 ctaaacggat tccaaagagt agaattgcat tgaccacgac tantttcaaa atgcttttta
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taaaaatgcc ctagcccact tcttacngca aggcacacct acacccctta tccccatact
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                                                                       240
                                                                       300
cctaqccatq qccatcccct tatgagcggg cgcagtgatt ataggctttc gctctaagat
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taaaaatgcc ctagcccact tcttaccaca aggcacacct acacccctta tccccatact
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aattcagtgt gcaaacatta tataaaaata gaaatactaa ctctacaggc agtatttcct
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gataaattat ttaaatagca tatctacnca atctgagata tctattccaa tggcaatgag
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ccattcattc acatgctcat ctgagaagac ttaagttctt ccagctttgg acaataactg
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cttttagaaa ctgtaaagta gttacaagag aacagttgcc caagactcag aatttttaaa
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aaaaaaaatg gagcatgtgt attatgtggc caatgtcttc actctaactt ggttatgaga
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gatgctc
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 aactgtccca aagtgctgct tcctaatagg aattcattaa cctaaaacaa gatgttacta
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 acacagtggc agtgttaaat gaagatgctg tctacaaggt agataatata ctgtttgata
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  tgctttgatg tgtcacataa agagtagttt gtagaaaatg ttggcacaat tttaacttct
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                                                                         240
  tgtttagtag tgtaaatgtt ctgggcaagt tttaatattt tgaatgcctt tggatattcc
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  agcaataaag gcatcatgtt ctgcaatagg atttcttact catttaccta ttttaacact
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420
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<213> Homo sapien

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tccaaaacta aggatgtcat tgcagttcac agtttgtata ataaataccc tccctttcaa
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gtaaagtttg caaataanga aattttttt aaaagtcctc agtaatctta ccagtaacaa
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                                                                         120
                                                                         151
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       <400> 454
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      <211> 515
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                                                                        60
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                                                                       120
gctttatgtg ttactgacac aatatcttcc tcaagctgat gggctttgga tgtagcatca
                                                                       180
ctgaacctct tcttaaactc ttcattttcc atttttaagc tttgtgttac ttcagtaaga
                                                                       240
cccttttgtt ctgcttgcag ttggtcacat ctttctttct catggttaag ttctctttcc
                                                                       300
attctcccaa cttgttctcg aagttgtgct gtttctttt ccagaacggc aattaacttt
                                                                       360
aacagttett ettetett catggttete teaatettea acteaagaag geetgettt
                                                                       420
gtggtcacca ctaacatgtc agaatttcct tcatcttcca tagtaagcag ctcttcaact
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                                                                       515
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      <211> 350
      <212> DNA
      <213> Homo sapien
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                                                                       120
acagtggctc agcctacaga gttccctata ggggaaagaa ggcaggaaat aggcgcaggg
                                                                       180
tetggteetg teeetgeace accetgagea getagtettg ggaagggatt acaggeetg
                                                                       240
ggccataggc tgctcgccat tctgctttcc tatcctgttt ctctccctgt gctgctccct
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      <211> 293
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      <213> Homo sapien
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aaagaggtgg acagagaaga cagcagagac catgggaccc ccctcagccc ctcctgcag attgcatgtc ccctggaagg aggtcctgct cacagcctca cttctaacct tctggaaccc acccaccact gccaagctca ctattgaatc cacgccattc aatgtcgcag aggggaagga ggttcttcta ctcgcccaca acctgcccca gaatcgtatt ggttacagct ggt	120 180 240 293
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<210> 459 <211> 394 <212> DNA <213> Homo sapien	
catatctaca tgtatgaact taacatggaa aatg	60 120 180 240 300 360 394
<210> 460 <211> 279 <212> DNA <213> Homo sapien	
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<211> 278

<212> DNA

180

240

278

. 120

### <213> Homo sapien

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  aaacatataa ctgaactcct cacacccaat tggaccaatc tatcacccta tagaagaact
  aatgttagta taaagtaaca tgaaaacatt ctcctccgca taagcctgcg tcagattaaa
  acactggact gacaattaac agccaatatc tacaatca
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 <211> 556
 <212> DNA
 <213> Homo sapiens
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 aatcactgtc ttgccccagg ctccggtgtg actcgtgcag ccatcgacag tgacgctgta 120
ggtgaagegg ctgttgeeet eggegeggat etegateteg ttggageeet ggaggageag 180
ggccttcttg aggttgccag tctgctggtc catgtaggcc acgctgttct tgcagtggta 240
ggtgatgttc tgggaggcct cggtggacat caggcgcagg aaggtcagct ggatggccac 300
ateggeaggg reggageest ggeegeeata etegaactgg aatecategg teatgetete 360
geogaaceeg acatgeetet tgteettggg gttettgetg atgtaceagt tettetggge 420
cacactgggc tgagtggggt acacgcaggt ctcaccagtc tccatgttgc agaagacttt 480
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agagtggcac atcttg
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 <211> 659
 <212> DNA
<213> Homo sapiens
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agtgcacgga agtcacaact ggtctatcag tccagacggg ggcctttggt caaatattct 180
tetgattaet tecaageece etetgaetae agataetaee eetaeeagte etteeagaet 240
ccacaacacc ccagcttect cttccaggac aagagggtgt cctggteect ggtetacete 300
cccaccatcc agagetgetg gaactaegge tteteetget eeteggaega geteeetgte 360
ctgggcctca ccaagtctgg cggctcagat cgcaccattg cctacgaaaa caaagccctg 420
atgctctgcg aagggctctt cgtggcagac gtcaccgatt tcgagggctg gaaggctgcg 480
attcccagtg ccctggacac caacageteg aagageacet ceteetteee etgeeeggea 540
gggcacttca acggcttccg cacggtcatc cgccccttct acctgaccaa ctcctcaggt 600
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<211> 695
<212> DNA
<213> Homo sapiens
<400> 464
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tcgaaggaat gccagctgca catcaaggac atcttcagga agttcaggat tgccgtagct 180
aaactgaaaa ccaccatcca tggactctcc aaaccaaacg tgtttcttct cagcactaga 240
atctgtccac cagtgtttcc gtggaacatt caaaggattg gcacttatgc atgtttcccc 300
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ggggttttta cgagaaccat caggactaat gaggctttct atttgtccat taacagactt 480
gagtgaagtc ataatctcat cggtgttgat tttgaaatcc attggttcat ctccataata 540
cggggcaaaa ccgccagctt tttcacctcc aatcccagca atggcagcgg ctccaacacc 600
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tggggagccc tcagatcctc tttcacctct gttac
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<211> 73
<212> DNA
<213> Homo sapiens
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ttcggtttcc agt
<210> 466
<211> 507
<212> DNA
<213> Homo sapiens
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tttaagtgta actgagaatc cgttaaatat gcccttgtac ttttggggggt ccacctgcat 240
acggcatttc actaaatcca ggggaaccac agcagtgtgt gtcagaccac aacttaagac 300
cccaccaaag ccacacagtg cataatactt cgcggagcca aattcacaac tgtactcttc 360
cacggcggcg gctgccaggt tgcgagggcg gcggggctgg cccgtgggcc ctggggagct 420
gctgcggagg tccccgagac catcgtgcac canctgcaga tgtggcgtgt tgaaggggtt 480
                                                                 507
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 <210> 467
 <211> 183
 <212> DNA
 <213> Homo sapiens
 <400> 467
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 cttctgagga gcaggaggga gccaccctcc ctgcagctac cctagctgag gagcctgttg 120
 tgaggggcag aatgagaaag gcaataaagg gagaaagaaa aaaaaaaaa aaaagggcgg 180
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 ccg
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 <211> 129
 <212> DNA
 <213> Homo sapiens
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<220>

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                                                                     129
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 <211> 243
 <212> DNA
 <213> Homo sapiens
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tttgaaaaga aatttcagtc tgagaaggca gcaggctcgg tgtccaagag cacgcagttt 180
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 ctg
                                                                    243
 <210> 470
 <211> 452
<212> DNA
<213> Homo sapiens
<400> 470
cctcaagtac gtccggcctg gtggtgggtt cgagcccaac ttcatgctct tcgagaagtg 60
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tcccagcgac gacgccaccg cgcttatgac cgaccccaag ctcatcacct ggtctccggt 180
gtgtcgcaac gatgttgcct ggaactttga gaagttcctg gtgggccctg acggtgtgcc 240
cctacgcagg tacagccgcc gcttccagac cattgacatc gagcctgaca tcgaagccct 300
gctgtctcaa gggctcagct gtgcctaggg cgccctcct accccggctg cttggcagtt 360
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ggaggaacac ctgatcttac agaaaatacc ac
                                                                    452
<210> 471
<211> 168
<212> DNA
<213> Homo sapiens
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<221> misc_feature
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cttcagcagc cgctcctaca cgagtgggcc cggttcccgc atcagctc
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<212> DNA
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<221> misc feature
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catgcagtgc ttcagcttca ttaagaccat gatgatcctc ttcaatttgc tcatctttct 180
gngtggcgca gccctgttgg cagcgggcat ctgggtgnca atcgatgggg catcctttct 240
gaagatette gggeeactgt egteeactge catgeagttt gteaasgngg getactteet 300
categoagee ggegttgtgg tntttgetet tggttteetg ggetgetatg gtgetaanae 360
tgagagcaag tgtgccctcg tgacgntctt cttcatcctc ctcctcntct tcattgctga 420
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<211> 69
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<213> Homo sapiens
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<213> Homo sapiens
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gtccagagag ccgcggcgcc tcgttccgag gagccatcgc cgaagcccga ggccgggtcc 120
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cgggttgggg actgcagggg aaggcagcgg tggcg
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 <211> 282
 <212> DNA
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 tcaaaagcca aaaaatggga gacaatttca catggacttt ggaaaatatt tttttccttt 180
 gcattcatct ctcaaactta gtttttatct ttgaccaacc gaacatgacc aaaaaccaaa 240
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 <210> 476
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 gctctgcatg atgctggcca ggacgccgaa gtccagcacg gtgctggcgt ccagcatgaa 240
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 gagategetg taggggtege egeegege egeeagetee ageaceeget eeegeageeg 360
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tgtacgagat ccctggactg gagcccatca cctttgcggg gaagatgcac ttcgtgccct 180
ggctggcgcg gccgatcttt ccgccctggg accgcggcta caaggaccca aggttctacc 240
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<213> Homo sapiens
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<210> 480
<211> 65
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<213> Homo sapiens
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65
ggagt
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<213> Homo sapiens
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gcaccaccac gaggcgattt gtgggccata ccaaggatgt gctgagtgtg gccttctcct 180
ctgacaaccg gcagattgtc tctggat
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<211> 319
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agtgcacgga agtcacaact ggtctatcag tccagacggg ggcctttggt caaatattct 180
tetgattact tecaageee etetgactae agatactace cetaceagtg ettecaaaet 240
gcacaacace enagettnet ettecagnae aagagggtgt eetggteeet ggeetacete 300
                                                                   319
cccaccatcc agagetgct
<210> 483
<211> 233
 <212> DNA
 <213> Homo sapiens
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 <221> misc_feature
 <222> (1)...(279)
 <223> n = A,T,C or G
 <400> 483
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cccgggcccg ctcctcaaca gtcaccgagc tgcggcggga gcagccccct tcagagctgc 180
 ccggcccagc actgggccct gccagggaca cnatatccga gctggcccgt gcc
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 <211> 194
 <212> DNA
 <213> Homo sapiens
 <400> 484
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 gatagatagc atgtaagggg gtggttgtcc caggaggcag ctgctgacag gtttgctaca 120
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<210> 486 <211> 70 <212> DNA <213> Homo	sapiens					
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF COLON CANCER AND METHODS FOR THEIR USE

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as colon cancer, are disclosed. Compositions may comprise one or more colon tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a colon tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as colon cancer. Diagnostic methods based on detecting a colon tumor protein, or mRNA encoding such a protein, in a sample are also provided.

### INTERNATIONAL SEARCH REPORT

Interne" anal Application No

PC1/US 99/30909 A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07 C12N15/62 C07K14/47 C07K16/18 C12N5/10 A61K38/02 A61K48/00 C12Q1/68 G01N33/50 G01N33/53 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) CO7K C12N C12Q G01N A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Category of LIU, W.L., ET AL.: "identification and 1,2,4-8X characterization of novel full-length cDNAs differentially expressed in human hematopoietic lineages" EMBL SEQUENCE DATA LIBRARY, 12 November 1998 (1998-11-12), XP002137433 heidelberg, germany accession no. AF097021 ADAMS, M.D., ET AL.: "initial assesment 1,2,4-8Х of human gene diversity and expression patterns based upon 83 Million Basepairs of cDNA sequence" EMBL SEQUENCE DATA LIBRARY, 18 April 1997 (1997-04-18), XP002137434 heidelberg, germany accession no. AA366895 -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents : "T" later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not cited to understand the principle or theory underlying the considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or

ments, such combination being obvious to a person skilled other means document published prior to the international filing date but "&" document member of the same patent family later than the priority date claimed Date of mailing of the international search report Date of the actual completion of the international search 21,08 00 19 May 2000 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Holtorf, S

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Inter 'ional Application No PC I /US 99/30909

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